PAXLOVID®

Nirmatrelvir; ritonavir

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Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

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Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic

5 May 2023 | Statement | Reading time: 7 min (1792 words)

The WHO Director-General has the pleasure of transmitting the Report of the fifteenth meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, held on Thursday 4 May 2023, from 12:00 to 17:00 CET.

During the deliberative session, the Committee members highlighted the decreasing trend in COVID-19 deaths, the decline in COVID-19 related hospitalizations and intensive care unit admissions, and the high levels of population immunity to SARS-CoV-2. The Committee's position has been evolving over the last several months. While acknowledging the remaining uncertainties posted by potential evolution of SARS-CoV-2, they advised that it is time to transition to long-term management of the COVID-19 pandemic.

The WHO Director-General concurs with the advice offered by the Committee regarding the ongoing COVID-19 pandemic. He determines that COVID-19 is now an established and ongoing health issue which no longer constitutes a public health emergency of international concern (PHEIC).

The WHO Director-General considered the advice provided by the Committee regarding the proposed Temporary Recommendations and issued them as per the below statement. The WHO Director-General will convene an IHR Review Committee to advise on Standing Recommendations for the long-term management of the SARS-CoV-2 pandemic, taking into account the 2023-2025 COVID-19 Strategic Preparedness and Response Plan. During this transition, States Parties are advised to continue following the issued Temporary Recommendations. The Director-General expressed his sincere gratitude to the Chair, the Members, and the Advisors of the Committee for their engagement and advice during the last three years.

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Proceedings of the meeting

The WHO Director-General, Dr Tedros Adhanom Ghebreyesus, welcomed Members and Advisors of the Emergency Committee, who were convened by videoconference. He noted that the number of weekly reported deaths and hospitalizations continue to decrease, but expressed concern that surveillance reporting to WHO has declined significantly, that there continues to be inequitable access to life-saving interventions, and that pandemic fatigue continues to grow. The Director-General announced the publication of the 2023-2025 COVID-19 Strategic Preparedness and Response Plan which is designed to guide countries in transitioning to long-term management of COVID-19. This plan outlines important actions for countries to consider for five areas: collaborative surveillance, community protection, safe and scalable care, access to countermeasures, and emergency coordination. The Director-General thanked Professor Houssin for his leadership in guiding the Committee over the last three years and each of the Committee Members and Advisors for their expertise, dedication, and commitment.

Foreword from the Director-General

Tedros Adhanom Ghebreyesus
Director-General, WHO

As the COVID-19 pandemic enters its fourth year, we have every reason for hope. At the time of writing, the number of weekly reported deaths is at its lowest since the pandemic began, and in most countries, life has returned to "normal". Still, millions continue to be infected or re-infected with SARS-CoV-2, thousands are still dying each week, and many questions remain about the potential emergence of new variants that could cause fresh surges.

At this moment of hope and uncertainty, WHO has updated its Global Strategic Preparedness, Readiness and Response Plan (SPRP) for the period 2023-2025. The previous plan, released in 2022, outlined two strategic objectives: to reduce the circulation of SARS-CoV-2; and to diagnose and treat COVID-19 to reduce mortality, morbidity and long-term sequelae.

This strategy retains those two objectives, and adds a third: to support countries as they transition from an emergency response to longer-term sustained COVID-19 disease prevention, control and management. This is a crucial step. We do not propose that countries abandon the ten pillars that served as a foundation for the pandemic response. Rather, the new strategy aligns these ten pillars with the five core components of equitable, inclusive and effective health emergency preparedness, response and resilience: collaborative surveillance, community protection, safe and scalable care, access to countermeasures, and emergency coordination.

In the wake of so much loss and disruption we must now restore, reinforce and strengthen health systems – which have been devastated – while sustaining the gains made during the pandemic. We must also continue to integrate COVID-19 surveillance and management into that for other respiratory diseases. WHO will continue supporting Member States as they make these adjustments.

I recognize that all countries are facing and fighting health threats other than COVID-19, and emergencies of different kinds. WHO understands that COVID-19 must be managed in the context of these other threats. We hope the new strategy will support the groundwork countries have laid and the momentum they have built to address the ongoing challenges posed by SARS-CoV-2.

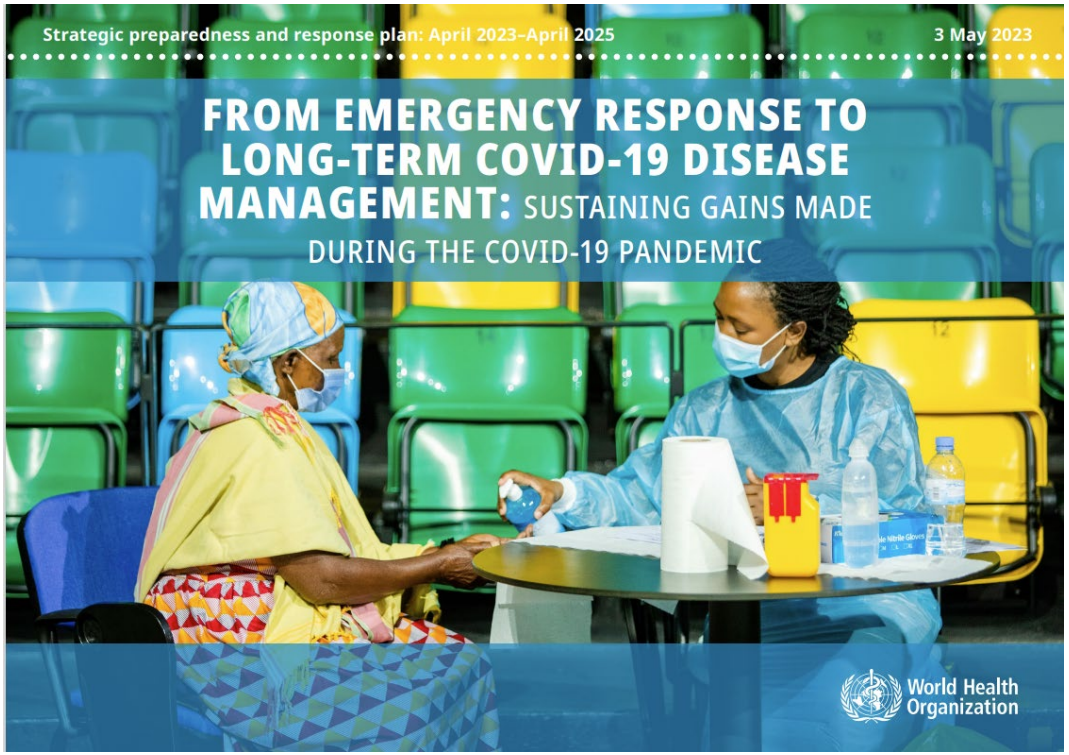
This is why we urge countries to maintain sufficient capacity, operational readiness and flexibility to scale up during surges of COVID-19, while maintaining other essential health services and preparing for the emergence of new variants with increased severity or capacity.

The new SPRP places strong emphasis on addressing post-COVID condition (also called long COVID), which appears to arise after as many as 6% of symptomatic COVID-19 cases. Research is key: we need to better understand post-COVID condition, including its risk factors and the role of immunity, and to develop methods to better quantify its burden. At the same time, countries need to strengthen and resource care pathways for this often debilitating condition.

WHO continues to work diligently and comprehensively to support all countries to address all aspects of COVID-19. It is my great hope that the hard lessons of COVID-19 will spur robust engagement in pandemic preparedness. The response to COVID-19 has been costly, but the cost will be greater if we fail to build on those investments by making a sustained commitment to science and public health.

Tedros Adhanom Ghebreyesus
Director-General, WHO

https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic . Acceso Mayo 2023;
From emergency response to long-term COVID-19 disease management: sustaining gains made during the COVID-19 pandemic (who.int). Acceso Mayo 2023



Strategic objectives

The underlying goal of the April 2023-April 2025 SPRP is to end the emergency phase of the COVID-19 pandemic in all countries and shift from emergency response to sustainable comprehensive management of COVID-19 within broader disease prevention and control programmes. This will be achieved by:

1) Reducing and controlling the incidence of SARS-CoV-2 variants with increased growth rates and immune escape, with a particular focus on reducing infections in high-risk and vulnerable populations;

2) Preventing, diagnosing and treating COVID-19 to reduce mortality, morbidity, and long-term sequelae; and

3) Supporting Member States' transition from crisis response to sustainable, integrated, longer-term and strengthened COVID-19 disease management.

The updated 2023-2025 COVID-19 strategy outlines practical, high-level actions that need to be sustained as response activities are adjusted to address the drivers of SARS-CoV-2 transmission and prioritizes activities that will continue to lessen the impact of the COVID-19 disease. Activities outlined in Annex II are organized to reflect management and integration of COVID-19 activities along the five core components of WHO's proposed global health architecture for health emergency preparedness, response and resilience. The components are emergency coordination, collaborative surveillance, community protection, safe and scalable care, and access to countermeasures.

The main approaches to achieving the goals and objectives continue to be through the access and optimal use of safe and effective tools:

- vaccination in at risk populations to prevent severe disease and death;
- early diagnosis, treatment and clinical care, especially in at-risk populations;
- integration of COVID-19 vaccination and COVID-19 disease management into existing primary health services;
- protecting health workers and other priority groups; and
- strong surveillance and monitoring of SARS-CoV-2 variants, including strategic and geographically representative sequencing to track known and future variants, respiratory pathogens, and other pandemic threats.

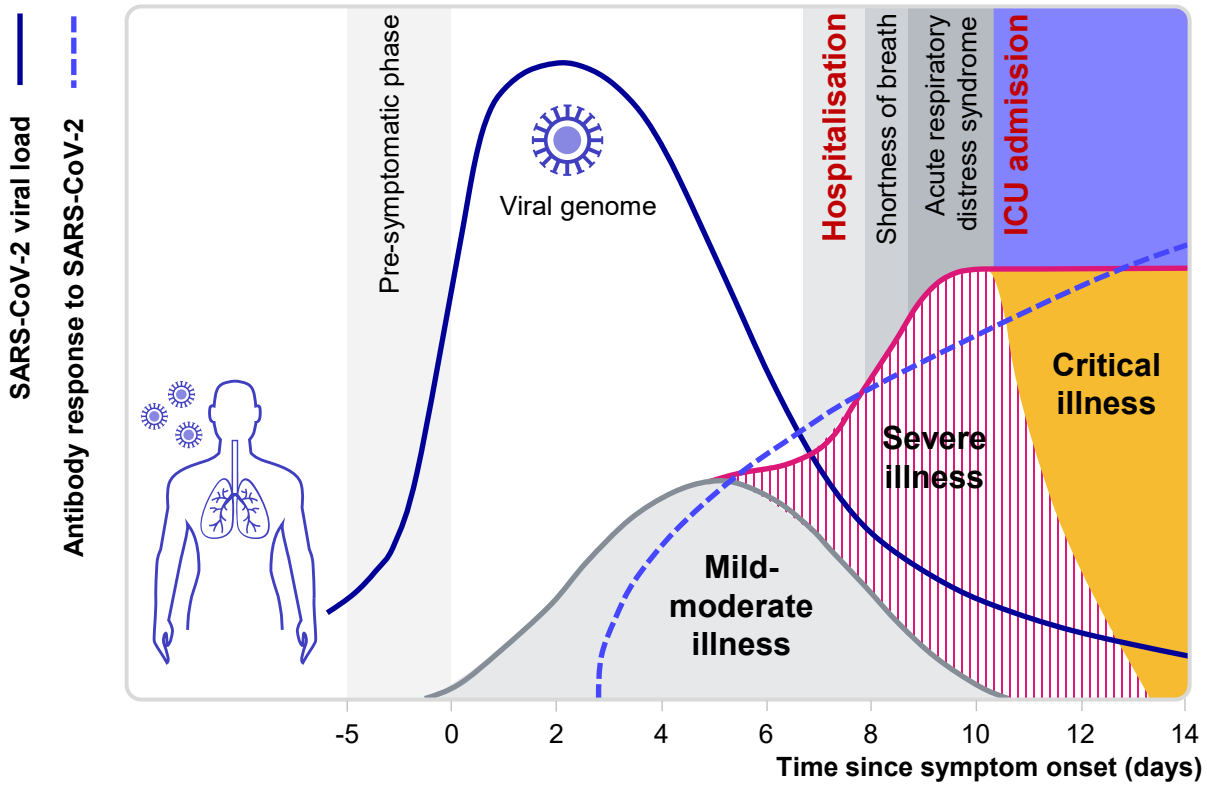
WHO wishes to encourage Member States to begin or continue using the WHO Partners Platform, a centralized vehicle for sharing preparedness, readiness and response actions that are being planned and implemented; identifying and updating resource needs; and tracking relevant contributions committed in the context of this pandemic.

"The underlying goal … is to end the emergency phase of the COVID-19 pandemic in all countries and shift from emergency response to sustainable comprehensive management of COVID-19"

From emergency response to long-term COVID-19 disease management: sustaining gains made during the COVID-19 pandemic (who.int). Acceso Mayo 2023

Los pacientes pueden progresar hacia la COVID-19 grave en una semana tras el inicio de los síntomas[1,2]

Defining High Risk



Source: Cevik, et al. 2020[2]

Severe illness develops **~1 week** after symptom onset[1]

Time from symptom onset to **death** ranges from **2–8 weeks**[1]

ICU, intensive care unit.

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Available at https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed: May 2023; 2. Cevik M, et al. Virology, transmission, and pathogenesis of SARS-CoV-2 *BMJ* 2020;371:m3862.

Aunque cualquiera puede verse afectado, hay factores de riesgo que predisponen a la progresión hacia la COVID-19 grave[1–3]

Defining High Risk

- Anyone can get COVID-19 and become seriously ill or die at any age[1]
- Certain risk factors elevate a person's risk of progression to severe COVID-19[1–3]

Age[1–3]

The strongest risk factor[2]

Risk

Risk of severe outcomes is increased in people who are ≥50 years; risk increases with age[2]

Age

Race & ethnicity[2]

People from racial and ethnic minority groups are more likely to experience severe COVID-19 at **younger ages**

***Barriers** to accessing healthcare support **are more common** in certain ethnic and racial minority groups*

Certain underlying conditions[1–3]

Risk

Death risk ratio increases with number of comorbid conditions[2]

Conditions

Male sex[3]

Male sex was associated with a higher risk of death, ARDS, admission to ICU, invasive ventilation, and cardiac abnormality in a meta-analysis of 61 studies[4]

Androgens may play a role in COVID-19 severity and progression[5]

Residents of LTCFs[3]

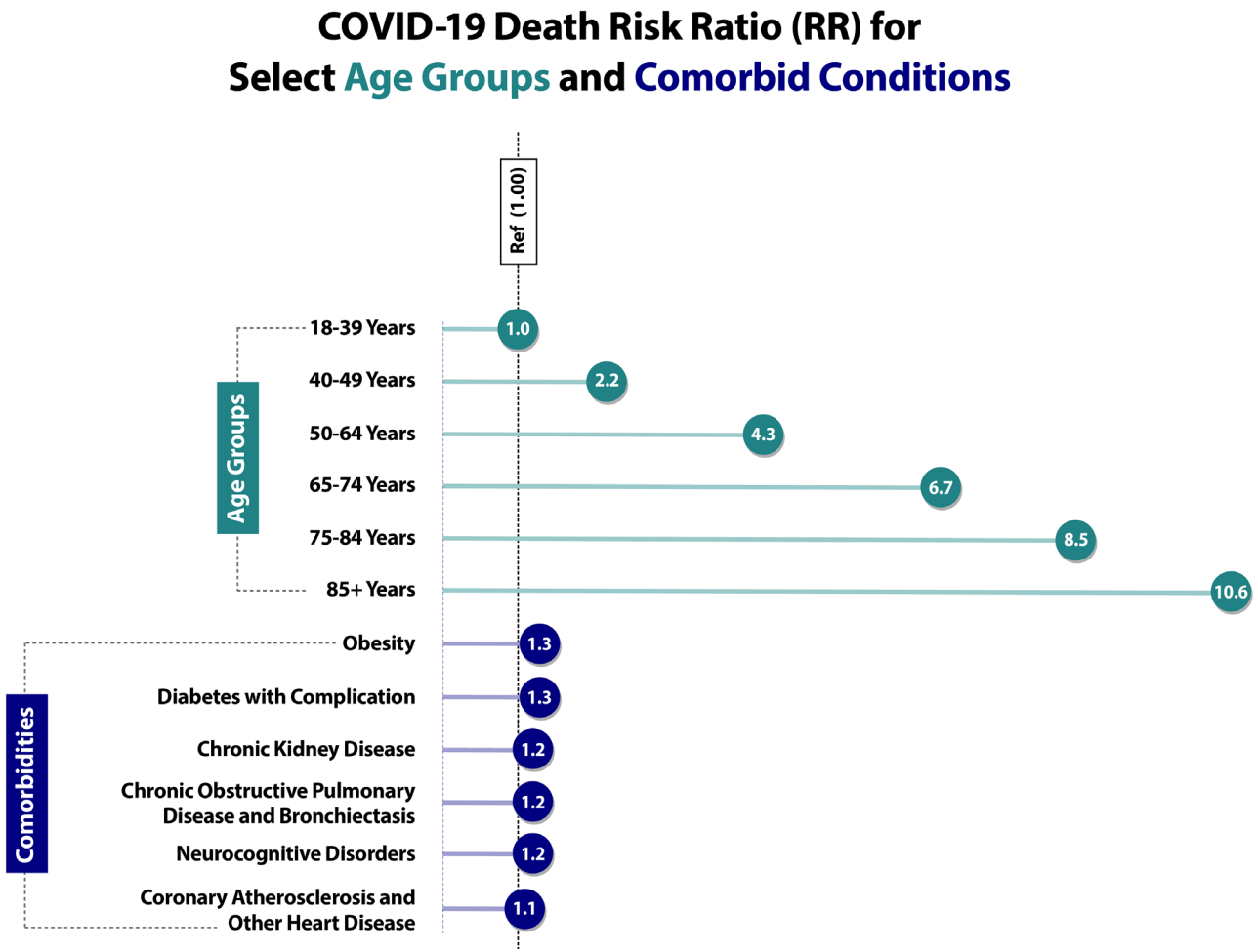
Residents of LTCFs are a vulnerable group associated with increased age and underlying health conditions

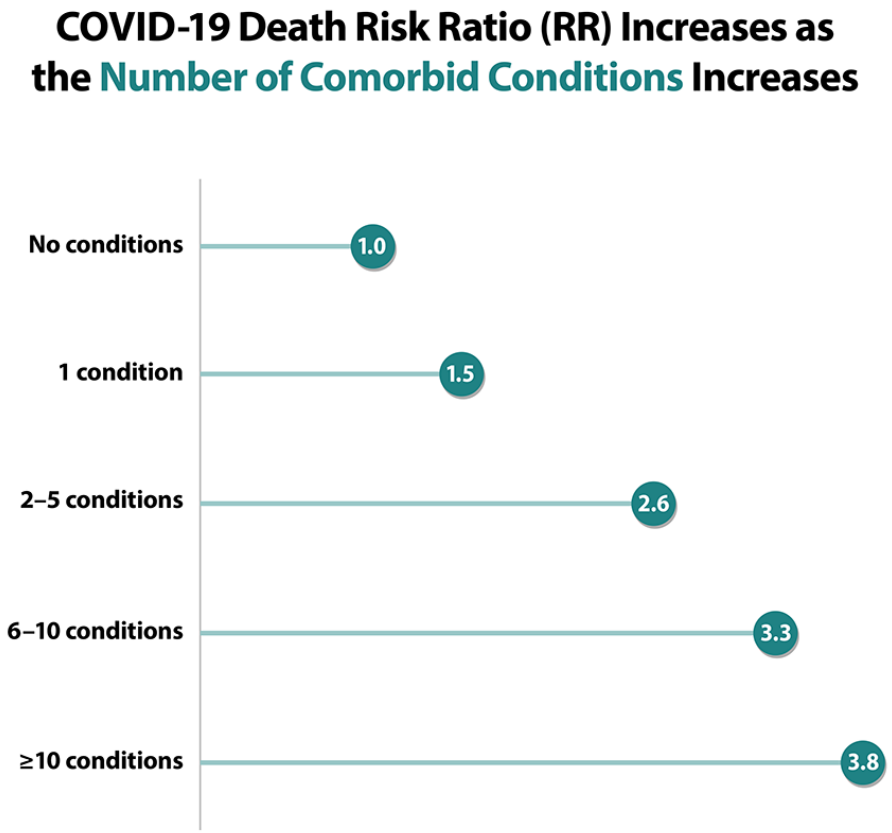
LTCFs are relatively closed and high-occupancy settings; COVID-19 outbreaks have spread rapidly, with high case fatality rates

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LTCF, long-term care facility.

1. World Health Organization. COVID-19 symptoms and severity. Available at: https://www.who.int/westernpacific/emergencies/covid-19/information/asymptomatic-covid-19 . Accessed: March 2023; 2. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed: March 2023; 3. European Centre for Disease Prevention and Control. Risk factors and risk groups. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups. Accessed: March 2023; 4. Fang W, et al. Aging (Albany NY). 2020;12(13):12493–12503; 5. Zong Z, et al. *Molecular Cancer*. 2021;20:76.

La edad y las comorbilidades juegan un papel esencial en la progresión hacia la COVID-19 grave



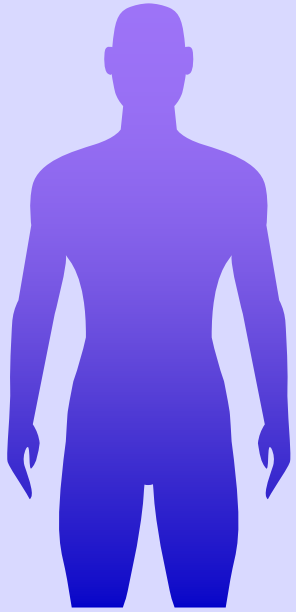


These data are based on multivariable generalized linear model analyses of more than 540,000 individuals.
COPD, chronic obstructive pulmonary disease; RR, risk ratio.
CDC. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html (Accessed May 2023).

Numerosas condiciones médicas están asociadas a un incremento en el riesgo de progresión hacia la COVID-19 grave

Defining High Risk

Non-exhaustive list of medical conditions associated with increased risk of progression to severe COVID-19[1,2]



- Cancer
- Cardiovascular disease
- Chronic kidney disease
- Chronic lung disease
- Diabetes
- Immunocompromised
- Obesity
- Neurological conditions

1. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html . Accessed: May 2023; 2. European Centre for Disease Prevention and Control. Risk factors and risk groups. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups. Accessed: May 2023.

La detección y tratamiento tempranos de la COVID-19 son esenciales para prevenir la enfermedad grave[1–5]

Treating Patients at High Risk

Patients can progress to severe COVID-19 within **1 week** of symptom onset[1,2]

Symptoms can deteriorate within **hours** of hospital admission[3]

Identifying patients at an **early stage** is of **paramount importance** in decision-making regarding follow-up, hospitalisation and treatment[3]

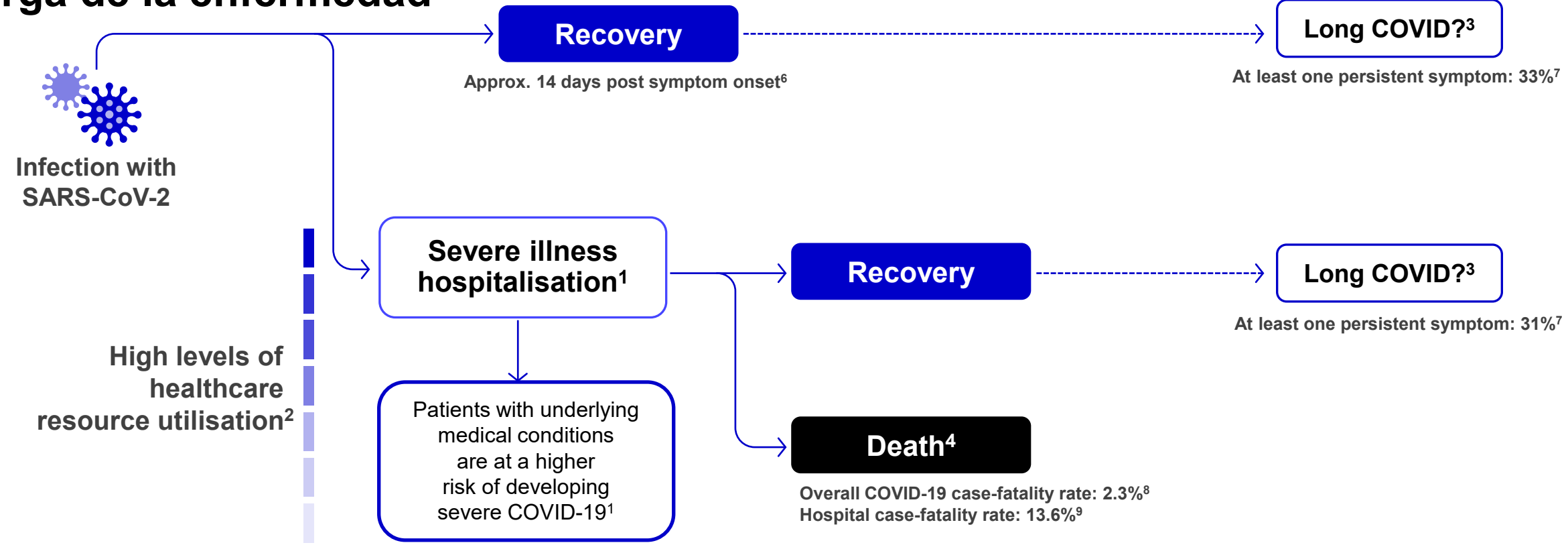
Treatment must be started **within days** after first developing symptoms to be effective[4]

Effective and early COVID-19 treatment will:[5]

- **Prevent hospitalisation and chronic sequelae**
- **Improve patient outcomes**
- **Help curb disease transmission**

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Available at https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed: May 2023; 2. Cevik M, et al. Virology, transmission, and pathogenesis of SARS-CoV-2 *BMJ* 2020;371:m3862; 3. Jakob CEM, et al. Infection 2022;50:359–70; 4. Centers for Disease Control and Prevention. COVID-19 Treatments and Medications. Available at: https://www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html. Accessed: May 2023; 5. Kim PS et al. Therapy for Early COVID-19 A Critical Need *JAMA* 2020;324(21):2149–50.

Carga de la enfermedad



SARS-CoV-2 infection can have a serious impact on patients and healthcare systems[1,2]
Early intervention minimises the potential for adverse outcomes[5]

1. CDC. COVID-19 People with Certain Medical Conditions. Available at: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (Accessed May 2023); 2. WHO. COVID-19 significantly impacts health services for noncommunicable diseases. Available at: www.who.int/news/item/01-06-2020-covid-19-significantly-impacts-health-services-for-noncommunicable-diseases (Accessed May 2023); 3. Ayoubkhani D, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ* 2021;372:n693; 4. Estiri H, et al. Individualized prediction of COVID-19 adverse outcomes with MLHO. *Sci Rep* 2021;11:5322; 5. Goyal DK, et al. Early intervention likely improves mortality in COVID-19 infection. *Clin Med* 2020;20(3):248–50; 6. WHO-China. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 2020: www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (Accessed May 2023); 7. Logue JK, et al. Sequelae in Adults at 6 Months After COVID-19 Infection. JAMA *Netw Open* 2021;4(2):e210830; 8. Wu Z, et al. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. *JAMA* 2020;323(13):1239–42; 9. . Di Fusco M, et al. Health outcomes and economic burden of hospitalized COVID-19 patients in the United States. *J Med Econ* 2021;24(1):308–17; 6. CDC. People with Certain Medical Conditions: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (Accessed May 2023).

Recomendaciones Guías para COVID-19 leve - moderado

World Health Organization

Nirmatrelvir/ ritonavir

- **Strong recommendation in favour**

Molnupiravir

- **Weak or conditional** recommendation **in favour**
- Mitigation strategies to reduce potential harms should be implemented

For those with highest risk of hospital admission

Remdesivir (intravenoso)

- **Weak or conditional** recommendation **in favour**

Sotrovimab

- **Strong recommendation against**
- New evidence has demonstrated that *in vitro* neutralisation of currently circulating SARS-CoV-2 variants is diminished

Figura creada a partir de BMJ. Living WHO Guideline on Drugs for COVID-19: www.bmj.com/content/370/bmj.m3379. (Accessed June 2023).

Recomendaciones SEIMC

TABLA 1. Tratamiento para pacientes de alto riesgo leve ambulatorios u hospitalizados por otra causa diferente a COVID-19

Fármacos por orden de prioridad según la recomendación del panel.

FÁRMACO	DOSIS	RECOMENDACIONES	PRECAUCIONES
Nirmatrelvir/Ritonavir	En los 5 primeros días de síntomas. Nirmatrelvir 300 mg con RTV 100 mg vo dos veces al día durante 5 días. *Necesario ajuste de dosis si disminución eFGR.	Insuficiencia renal: · Si eFGR>60 ml: sin cambios. · Si eFGR 30-60ml/min: Nirmatrelvir 150 mg con RTV 100 mg PO dos veces al día. · Si eFGR <30: no recomendado. · Insuficiencia hepática grave (Child-Pugh C): no recomendado.	No iniciar sin revisar interacciones.
Remdesivir	En los 7 primeros días de síntomas. RDV 200 mg iv el día 1, seguido de RDV 100 mg IV una vez al día los días 2 y 3.	Contraindicado si FG <30 ml/min.	Riesgo de elevación transitoria de enzimas hepáticas.
Anticuerpos monoclonales		Valorar en cada momento. Se recomienda sólo si son activos frente a las variantes circulantes.	
Dexametasona			No está indicada.

*Es probable que los individuos vacunados que no hayan recibido una dosis de refuerzo de la vacuna COVID-19 tengan un mayor riesgo de padecer una enfermedad grave.

TABLA 2.

Grupos de riesgo para priorizar el uso de fármacos ANTI-SARS-CoV-2

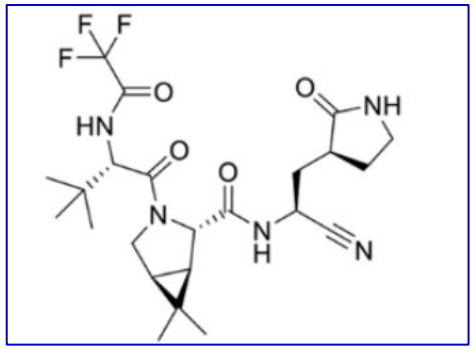
Personas con inmunosupresión grave	No se espera una respuesta inmune adecuada a la vacunación.
Pacientes con más 65 años independiente del estado vacunal	

Tabla extraída de Recomendaciones SEIMC para el manejo clínico de pacientes con COVID-19 – SEIMC – COVID-19. (Accesed June 2023)

¿Qué es PAXLOVID?

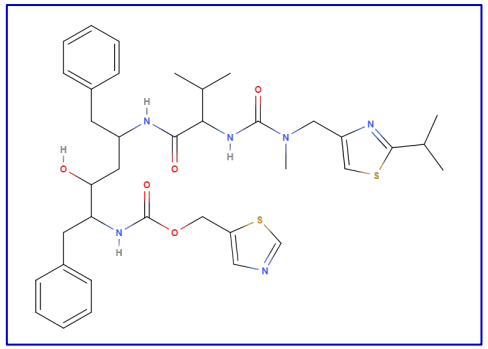
Inhibidor de la proteasa[1]

Nirmatrelvir
(PF-07321332)[1]



+

Ritonavir[2-3]

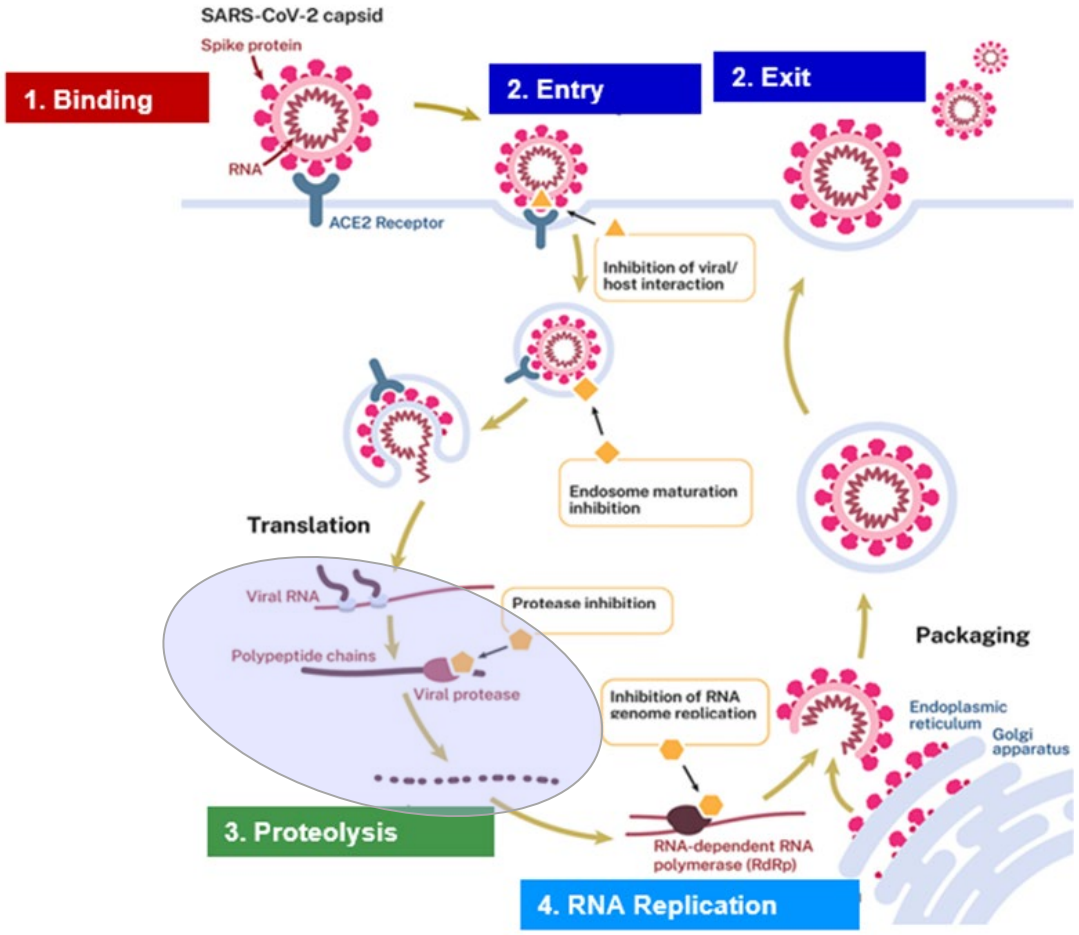


Antiretroviral. Potenciador farmacocinético[2-3]

Indicado para el tratamiento oral de la enfermedad por COVID 19 en adultos (18 años de edad y mayores) que no requieren aporte de oxígeno suplementario y que tienen un riesgo alto de progresar a COVID 19 grave[4]

1. Owen DR, et al. An oral SARS-CoV-2 M pro inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021. 2021 Dec 24;374(6575):1586-1593.
2. NORVIR Prescribing Information. Available from: FICHA TECNICA NORVIR 100 mg COMPRIMIDOS RECUBIERTOS CON PELICULA (aemps.es) Accessed Mayo 2023;
3. Cooper, CL et al. A review of low-dose ritonavir in protease inhibitor combination therapy. Clin Infect Dis 2003;36(12):1585–92.
4. Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

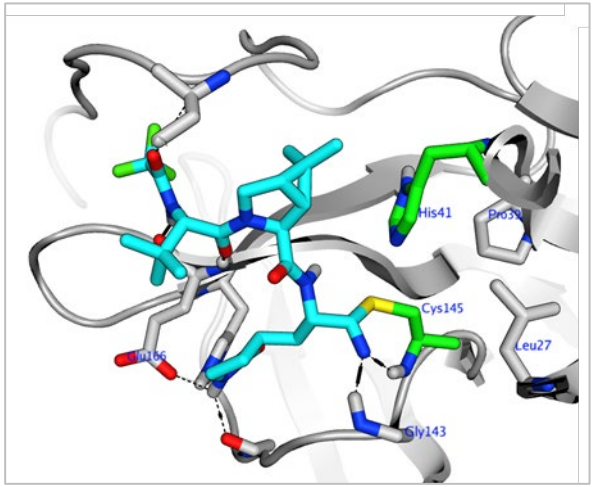
Nirmatrelvir Inhibe la Proteólisis de SARS-CoV-2



Eastman RT, et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS Central Science. 2020;6:672–83

Nirmatrelvir es un inhibidor peptidomimético de la proteasa principal del SARS-CoV-2 (Mpro), también conocida como proteasa 3C-like (3CLpro) o proteasa nsp5. La inhibición de la Mpro del SARS-CoV-2 hace que la proteína sea incapaz de procesar precursores poliproteicos, lo que impide la replicación viral.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023



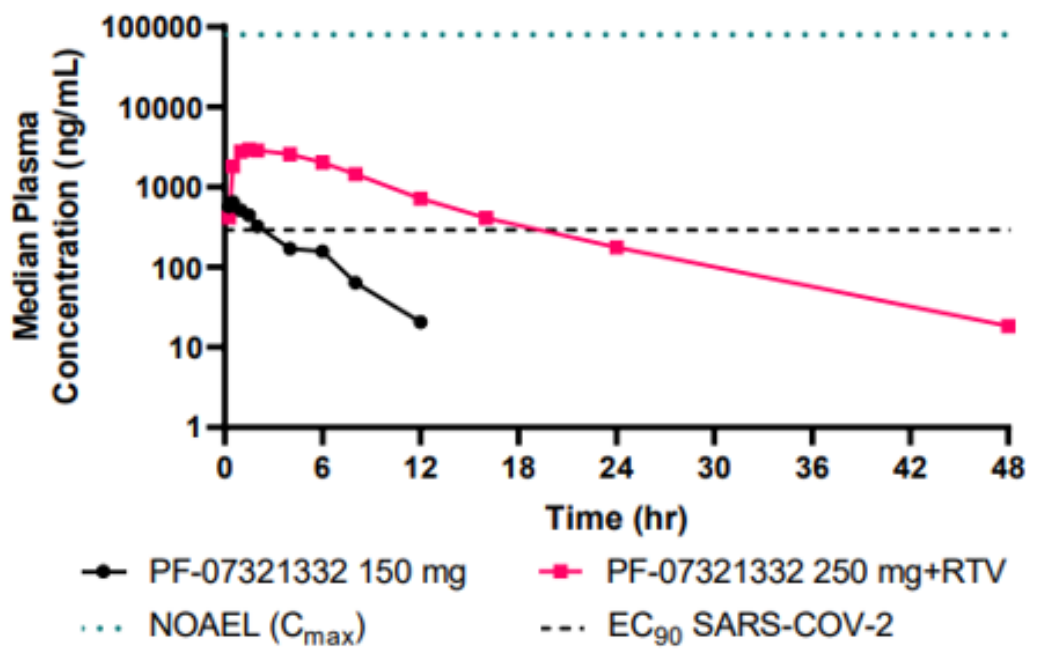
Owen DR, et al. An oral SARS-CoV-2 M pro inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021. 2021 Dec 24;374(6575):1586-1593.

Co-administración de Nirmatrelvir con ritonavir (RTV)

Ritonavir as a PK enhancer

- RTV enhances the bioavailability of PF-07321332 by slowing its metabolism by CYP3A4[1]
  - RTV (100 mg q12hr) is not expected to have any antiviral activity against SARS-CoV-2[2]

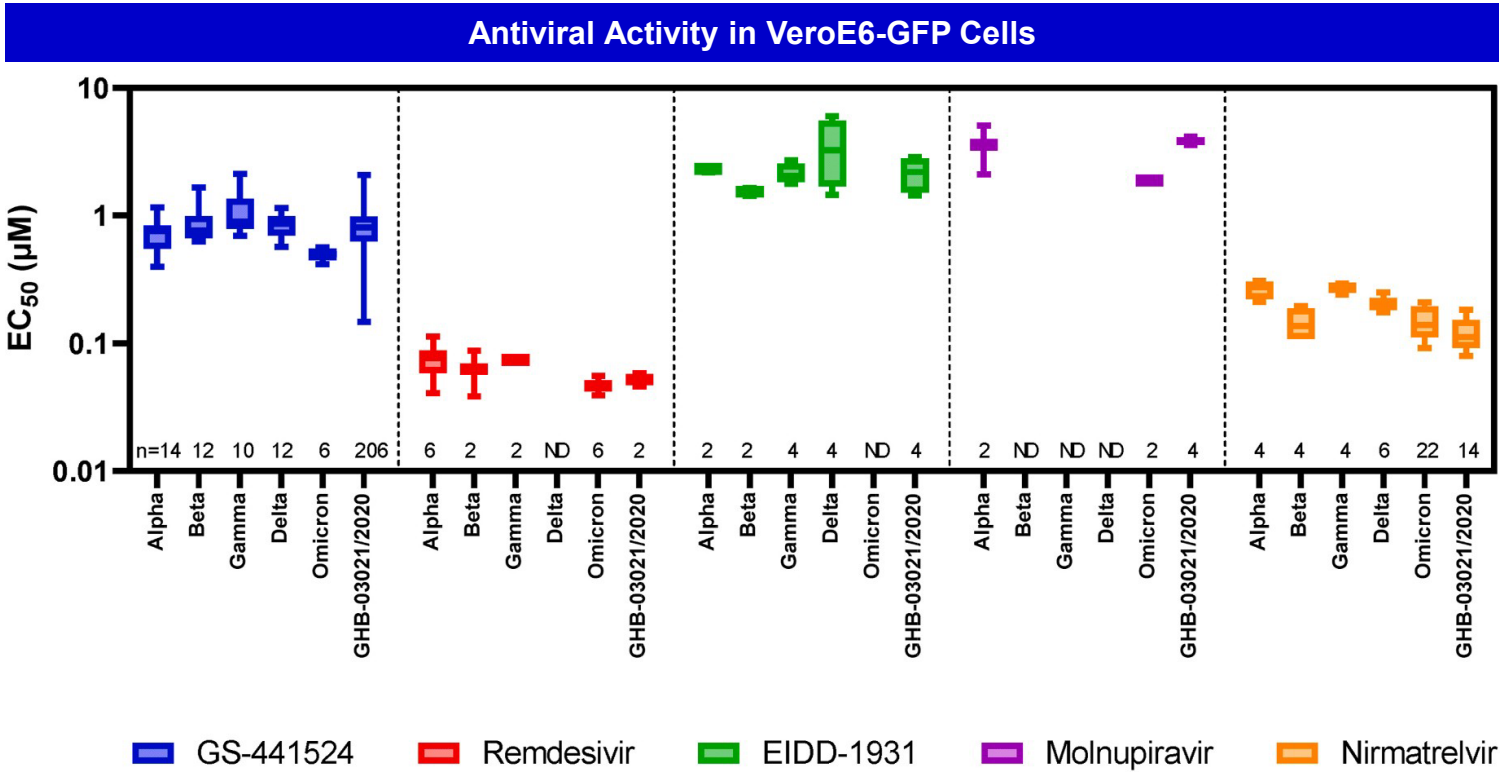
Graph to illustrate PK Enhancer Concept



C_{max}, maximum concentration; CYP, cytochrome P450; EC_{90}, 90% effective concentration; NOAEL, no observed adverse effect level; PK, pharmacokinetic; q12h, every 12 hours.

1. Cooper, CL et al. A review of low-dose ritonavir in protease inhibitor combination therapy. Clin Infect Dis 2003;36(12):1585–92; 2. Owen DR, et al. An oral SARS-CoV-2 M pro inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021. 2021 Dec 24;374(6575):1586-1593.

Eficacia *in vitro* de nirmatrelvir frente a la variante Ómicron



Adapted from: Vangeel L, et al. Antiviral Research 2022;198:105252.

- Nirmatrelvir potently inhibited both wild-type and mutated M^{pro} with a mean K_i (ability to bind to an enzyme) of 0.933 nM and 0.635 nM, respectively (P=0.07; not significantly different)
- Comparison of the SARS-CoV-2 Omicron P132H M^{pro} crystal structure with the wild-type M^{pro} shows that the binding mode of nirmatrelvir is the same in both structures
- This study demonstrated the *in vitro* inhibitory activity of nirmatrelvir against the Omicron variant M^{pro}, and indicates the structural basis for the retention of *in vitro* potency against the mutant protein
- **These data suggest that nirmatrelvir/ritonavir has the potential to maintain plasma concentrations of nirmatrelvir many-fold times higher than the amount required to stop the SARS-CoV-2 variant, Omicron, from replicating in cells**
- The study also reports on methods for assessing activity against future variants with mutated M^{pro}

Greasley SE, et al. Structural basis for Nirmatrelvir in vitro efficacy against SARS-CoV-2 Variants *J Biol Chem* 2022;298(6):101972.

PAXLOVID ®: Desarrollo clínico

EPIC-HR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

ABSTRACT

BACKGROUND

Nirmatrelvir is an orally administered severe acute respiratory syndrome coronavirus 2 main protease (M^{pro}) inhibitor with potent pan–human-coronavirus activity in vitro.

METHODS

We conducted a phase 2–3 double-blind, randomized, controlled trial in which symptomatic, unvaccinated, nonhospitalized adults at high risk for progression to severe coronavirus disease 2019 (Covid-19) were assigned in a 1:1 ratio to receive either 300 mg of nirmatrelvir plus 100 mg of ritonavir (a pharmacokinetic enhancer) or placebo every 12 hours for 5 days. Covid-19–related hospitalization or death from any cause through day 28, viral load, and safety were evaluated.

RESULTS

A total of 2246 patients underwent randomization; 1120 patients received nirmatrelvir plus ritonavir (nirmatrelvir group) and 1126 received placebo (placebo group). In the planned interim analysis of patients treated within 3 days after symptom onset (modified intention-to treat population, comprising 774 of the 1361 patients in the full analysis population), the incidence of Covid-19–related hospitalization or death by day 28 was lower in the nirmatrelvir group than in the placebo group by 6.32 percentage points (95% confidence interval [CI], −9.04 to −3.59; P<0.001; relative risk reduction, 89.1%); the incidence was 0.77% (3 of 389 patients) in the nirmatrelvir group, with 0 deaths, as compared with 7.01% (27 of 385 patients) in the placebo group, with 7 deaths. Efficacy was maintained in the final analysis involving the 1379 patients in the modified intention-to-treat population, with a difference of −5.81 percentage points (95% CI, −7.78 to −3.84; P<0.001; relative risk reduction, 88.9%). All 13 deaths occurred in the placebo group. The viral load was lower with nirmaltrelvir plus ritonavir than with placebo at day 5 of treatment, with an adjusted mean difference of −0.868 $\log_{10}$ copies per milliliter when treatment was initiated within 3 days after the onset of symptoms. The incidence of adverse events that emerged during the treatment period was similar in the two groups (any adverse event, 22.6% with nirmatrelvir plus ritonavir vs. 23.9% with placebo; serious adverse events, 1.6% vs. 6.6%; and adverse events leading to discontinuation of the drugs or placebo, 2.1% vs. 4.2%). Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) occurred more frequently with nirmatrelvir plus ritonavir than with placebo.

CONCLUSIONS

Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe Covid-19 that was 89% lower than the risk with placebo, without evident safety concerns. (Supported by Pfizer; ClinicalTrials.gov number, NCT04960202.)

Hammond J et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. Covid-19 N Engl J Med 2022 Apr 14;386(15):1397-1408.

EPIC-HR: criterios de inclusión

- ≥18 years of age
- Confirmed SARS-CoV-2 infection as determined by RT-PCR within 5 days prior to randomisation
- Initial onset of COVID-19 signs / symptoms within 5 days prior to the day of randomisation
- At least ≥1 COVID-19 signs / symptoms present at time of study entry
- Participant has ≥1 condition or characteristic that is associated with an increased risk of developing severe COVID-19:

Conditions associated with increased risk of severe COVID-19	
• ≥60 years of age • BMI >25 kg/m² • Cigarette smoking • Immunosuppressive disease (including HIV infection with CD4 cell count <200 mm^3 and viral load <400 copies/mL) or prolonged iatrogenic immunosuppression • Chronic lung disease • Cardiovascular disease	• Kidney disease • Sickle cell disease • Hypertension • Diabetes • Cancer • Neurodevelopmental disorders or other medically complex conditions • Medical-related technological dependence

RT-PCR, reverse-transcription polymerase chain reaction.

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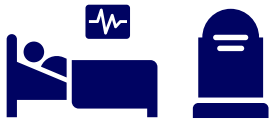
EPIC-HR: Resultados y conclusiones

Efficacy of oral administration of nirmatrelvir (300 mg) with ritonavir (100 mg) every 12 hours for 5 days:



COVID-19 hospitalization or death from any cause

Treatment 3 days after symptom onset

88.9% RRR

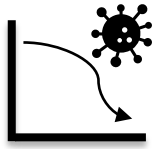
Treatment 5 days after symptom onset

87.8% RRR

0 deaths in treatment group
vs.
13 deaths in placebo group

Efficacy was **supported by subgroup analyses regardless of**

- **Age**
- **Sex**
- **Race**
- **BMI**
- **Baseline serology status**
- **Viral load**
- **Coexisting conditions**
- **Number of coexisting conditions at baseline**



Treatment with nirmatrelvir plus ritonavir was also associated with an additional **reduction in SARSCoV-2 viral load at day 5, by a factor of 10,** as compared with placebo.

Dysgeusia, diarrhea, and vomiting were the **most frequent adverse events** occurring more often in recipients of nirmatrelvir plus ritonavir.

Treatment with nirmatrelvir plus ritonavir early in Covid-19 illness can decrease progression to severe disease and quickly reduce SARS-CoV-2 viral load

Hammond J et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. Covid-19 N Engl J Med 2022 Apr 14;386(15):1397-1408.

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Sustained Alleviation and Resolution of Targeted COVID-19 Symptoms With Nirmatrelvir/Ritonavir Versus Placebo

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BACKGROUND AND OBJECTIVES

- More than 600 million cumulative cases and 6.5 million deaths due to COVID-19 have been reported globally.[1]
- Severe cases of COVID-19 are associated with hospitalization, intensive care unit admission, invasive mechanical ventilation, or death.[2,3]
- Nirmatrelvir, a potent inhibitor of the SARS-CoV-2 3-chymotrypsin-like cysteine protease (M^{pro}), is an oral antiviral COVID-19 treatment that is coadministered with pharmacokinetic-boosting agent ritonavir (nirmatrelvir/ritonavir; PAXLOVID™, Pfizer Inc) and approved in the United States under emergency use authorization.[4,5]
- EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) was a phase 2/3 study evaluating nirmatrelvir/ritonavir 300 mg/100 mg twice daily in adults with mild to moderate COVID-19 at increased risk of progression to severe disease.[6]
  - Previously published results from EPIC-HR demonstrated an 88% relative risk reduction against COVID-19–related hospitalization or all-cause mortality through Day 28 when treatment was initiated within 5 days of symptom onset.[7]
- Here, we report additional secondary endpoints from EPIC-HR including time to sustained symptom alleviation and time to sustained symptom resolution through Day 28 in nonhospitalized symptomatic adult patients with COVID-19 who are at an increased risk of progression to severe disease.

METHODS

- In this phase 2/3 double-blind study (NCT04960202), eligible adults 18 years or older were randomized 1:1 to receive nirmatrelvir/ritonavir 300 mg/100 mg or placebo every 12 hours for 5 days (10 doses total).
- Patients were eligible for the study if they had confirmed SARS-CoV-2 infection from a specimen collected within 5 days of randomization, initial onset of COVID-19 signs/symptoms within 5 days before the day of randomization, ≥1 prespecified COVID-19 sign/symptom on the day of randomization, and ≥1 characteristic or underlying prespecified medical condition associated with increased risk of developing severe COVID-19 and had not received or were not expecting to receive any dose of a COVID-19 vaccine before the Day 34 visit.
- Efficacy endpoints were assessed as of the date of last patient last visit (April 26, 2022) for the following populations described in **Table 1**. The results presented herein focus on the modified intent-to-treat 1 (mITT1) population; in general, similar results were obtained for the mITT and mITT2 analysis sets.

Table 1. Analysis Populations

Population	Definition
mITT	All participants randomly assigned to study intervention who received ≥1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated within 3 days of COVID-19 onset.
mITT1	All participants randomly assigned to study intervention who received ≥1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
mITT2	All participants randomly assigned to study intervention who received ≥1 dose of study intervention, including those who did or were expected to receive therapeutic mAbs.

mAb=monoclonal antibody; mITT=modified intent-to-treat; mITT1=modified intent-to-treat 1; mITT2=modified intent-to-treat 2.

- A subset of the full signs/symptoms collected were identified as "targeted" signs/symptoms and were included in the analyses. The targeted signs and symptoms attributable to COVID-19 were evaluated per prespecified US Food and Drug Administration guidelines[8] and were selected from cough, shortness of breath or difficulty breathing, fever (documented temperature ≥38°C [100.4°F]) or subjective fever, feeling feverish, chills or shivering, fatigue (low energy or tiredness), muscle or body aches, diarrhea (loose or watery stools), nausea (feeling like you wanted to throw up), vomiting (throw up), headache, sore throat, stuffy or runny nose, loss of smell, and loss of taste (**Figure 1**).
- Patients logged the presence and severity on 3- or 4-point scales of the 15 prespecified COVID-19 signs/symptoms at approximately the same time daily from Day 1 (before dose) through Day 28 using an electronic handheld device.
- Study outcomes are described in **Table 2**.

Table 2. Description of Sustained Alleviation and Sustained Resolution of All Targeted COVID-19 Signs/Symptoms

Outcome	Definition
Sustained alleviation	• The event occurring on the first of 4 consecutive days when all symptoms scored as moderate or severe at study entry were scored as mild or absent AND all symptoms scored mild or absent at study entry were scored as absent. • The first day of the 4 consecutive-day period was considered the First Event Date.
Sustained resolution	• The event occurring when all targeted symptoms were scored as absent for 4 consecutive days. • The first day of the 4 consecutive-day period was considered the First Event Date.

METHODS (continued)

- Times to sustained alleviation and resolution of all targeted signs/symptoms were assessed through Day 28 using the following analytical methods:
  - A Cox proportional hazard regression model where the estimate of the hazard ratio for treatment (nirmatrelvir/ritonavir vs placebo), its confidence interval (CI), and p value were assessed.
  - Kaplan-Meier analysis where tabular summaries of the Kaplan-Meier curves provided the median, quartiles, and range for each treatment group.
  - All missing efficacy data at baseline except for time to event endpoints were treated as mild. A baseline observation carried forward approach was used for missing data for participants discontinued due to an adverse event or lack of efficacy. The last observation carried forward method was used for other missing data.
- Individual signs/symptoms were compared between groups using descriptive analyses.

RESULTS

- Of the 2246 patients enrolled in EPIC-HR, 2085 (nirmatrelvir/ritonavir 300 mg/100 mg, n=1039; placebo, n=1046) met criteria for the mITT1 population.
- Demographic and baseline clinical characteristics within the mITT1 population were similar between the nirmatrelvir/ritonavir and placebo groups (**Table 3**).

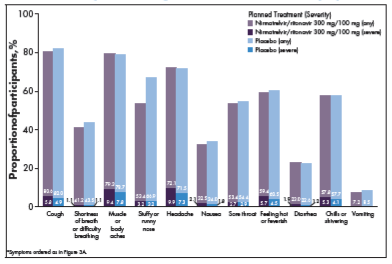
Table 3. Demographics and Baseline Characteristics (mITT1 Analysis Set)

Characteristic	Nirmatrelvir/Ritonavir 300 mg/100 mg (n=1039)	Placebo (n=1046)
Median (range) age, y	45.0 (18.0–86.0)	47.0 (18.0–88.0)
Male	520 (50.0)	506 (48.4)
Race, n (%)		
White	738 (71.0)	749 (71.6)
Black or African American	50 (4.8)	44 (4.2)
Asian	146 (14.1)	149 (14.2)
American Indian or Alaska Native	95 (9.1)	93 (8.9)
Mean duration since first symptom, d (SD)	2.9 (1.1)	3.0 (1.1)
Number of risk factors for severe COVID-19, n (%)		
1	414 (39.8)	395 (37.8)
2	359 (34.6)	380 (36.3)
3	177 (17.0)	176 (16.8)
4	71 (6.8)	73 (7.0)
>4	16 (1.5)	22 (2.1)
SARS-CoV-2 serology (IgM, IgG) status, n (%)		
Negative	487 (46.9)	505 (48.3)
Positive	540 (52.0)	528 (50.5)

IgG=immunoglobulin G; IgM=immunoglobulin M; mITT1, modified intent-to-treat 1; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

- Symptoms present at baseline are shown in **Figure 1**.

Figure 1. Cough, headache, and muscle or body aches were the most common symptoms at baseline, with headache and muscle or body aches being the most common severe symptoms*

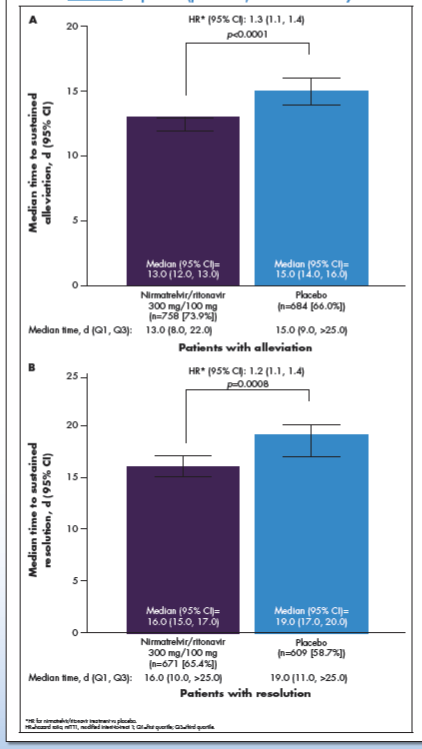


*Symptoms ordered as in Figure 3A.

RESULTS (continued)

- A greater number of patients achieved sustained alleviation and sustained resolution with nirmatrelvir/ritonavir 300 mg/100 mg compared with placebo.
  - A shorter median time to sustained alleviation was observed with nirmatrelvir/ritonavir 300 mg/100 mg (13 days) compared with placebo (15 days; p<0.0001; **Figure 2A**).
  - Similarly, a shorter median time to sustained resolution was observed with nirmatrelvir/ritonavir 300 mg/100 mg (16 days) vs placebo (19 days; p=0.0008; **Figure 2B**).

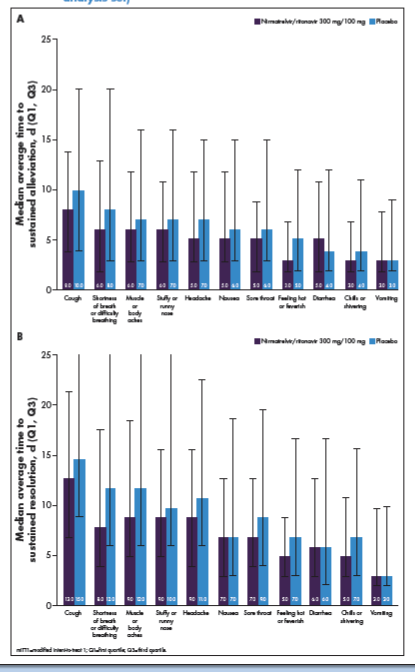
Figure 2 Nirmatrelvir/ritonavir treatment resulted in a (A) 2-day improvement in time to symptom alleviation vs placebo (p<0.0001) and (B) 3-day improvement in time to symptom resolution vs placebo (p≥0.0008) in the mITT1 analysis set



*HR for nirmatrelvir/ritonavir treatment vs placebo. HR=hazard ratio; mITT1, modified intent-to-treat 1; Q1=first quartile; Q3=third quartile.

- The median times to sustained alleviation and resolution were shorter for nirmatrelvir/ritonavir compared with placebo for most individual signs and symptoms.
  - Nonsevere cough, feeling hot or feverish, headache, and shortness of breath or difficulty breathing symptoms showed shorter times to both sustained alleviation and resolution in patients treated with nirmatrelvir/ritonavir compared with placebo (**Figure 3**).
  - The median time to sustained alleviation and sustained resolution of both cough and headache was 2 days less with nirmatrelvir/ritonavir 300 mg/100 mg compared with placebo (**Figure 3**).
  - The median times to sustained resolution of muscle or body aches and shortness of breath or difficulty breathing were 3 days and 4 days less, respectively, with nirmatrelvir/ritonavir (**Figure 3B**).
  - In both nirmatrelvir/ritonavir and placebo groups, vomiting, feeling hot/feverish, and chills/shivering were alleviated faster than other targeted signs/symptoms, whereas cough, shortness of breath or difficulty breathing, and muscle or body aches lasted longer (**Figure 3A**).

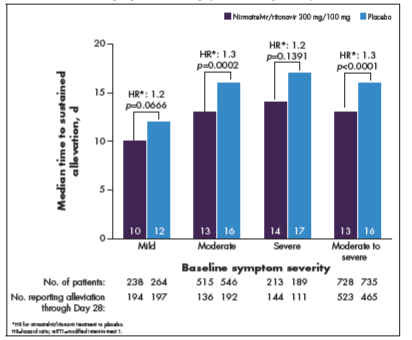
Figure 3. Nirmatrelvir/ritonavir treatment resulted in faster (A) alleviation and (B) resolution of all individual symptoms vs placebo with the exception of GI-related symptoms (mITT1 analysis set)



mITT1=modified intent-to-treat 1; Q1=first quartile; Q3=third quartile.

- The median times to sustained alleviation were shorter for nirmatrelvir/ritonavir compared with placebo regardless of baseline severity (**Figure 4**).
  - Among the patients who had moderate to severe symptoms at baseline (nirmatrelvir/ritonavir, n=728; placebo, n=735), the median time to sustained alleviation was significantly shorter with nirmatrelvir/ritonavir (13 days) vs placebo (16 days; p<0.0001).

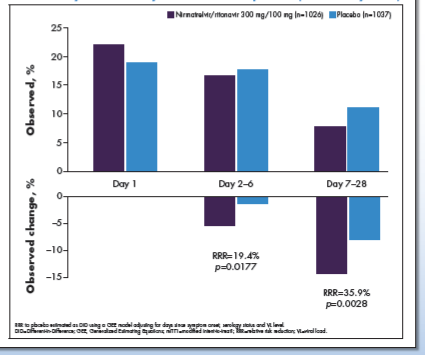
Figure 4. Patients treated with nirmatrelvir/ritonavir achieved sustained alleviation of COVID-19 symptoms regardless of baseline symptom severity (mITT1 analysis set)



*HR for nirmatrelvir/ritonavir treatment vs placebo. HR=hazard ratio; mITT1=modified intent-to-treat 1.

- The proportion of patients with severe signs/symptoms in the nirmatrelvir/ritonavir compared with placebo group was substantially higher at baseline but significantly lower after treatment and during the follow-up period (Day 7 to Day 28), indicating that nirmatrelvir/ritonavir 300 mg/100 mg significantly reduced symptom severity through Day 28 (**Figure 5**).

Figure 5. Treatment with nirmatrelvir/ritonavir significantly reduced the percentage of patients with severe signs or symptoms from Days 2–6 and Days 7–28 relative to placebo (mITT1 analysis set)



RRR=relative risk reduction; vL=viral load.

CONCLUSIONS

- **Nirmatrelvir/ritonavir 300 mg/100 mg treatment reduced duration of COVID-19 symptoms compared with placebo in adult patients at high risk of progressing to severe disease, shortening the time to symptom alleviation and resolution by 2–3 days.**
- **Nirmatrelvir/ritonavir 300 mg/100 mg treatment significantly reduced severe COVID-19 symptoms relative to placebo.**

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DISCLOSURES

Jennifer Hammond, Heidi Leister-Tebbe, Annie Gardner, Paula Abreu, Weihang Bao, Wayne Wisemandle, Wajeeha Ansari, Magdalena Alicja Harrington, Rienk Pypstra, and James M. Rusnak are employees of Pfizer Inc and may hold stock or stock options. Kara W. Chew reports research grant funding to the institution from Merck Sharp & Dohme and has consulted for Pardes Biosciences. Abraham Simón-Campos reports personal fees from AstraZeneca and Roche.

Presented at IDWeek 2022; October 19–23, 2022; Washington, DC, USA

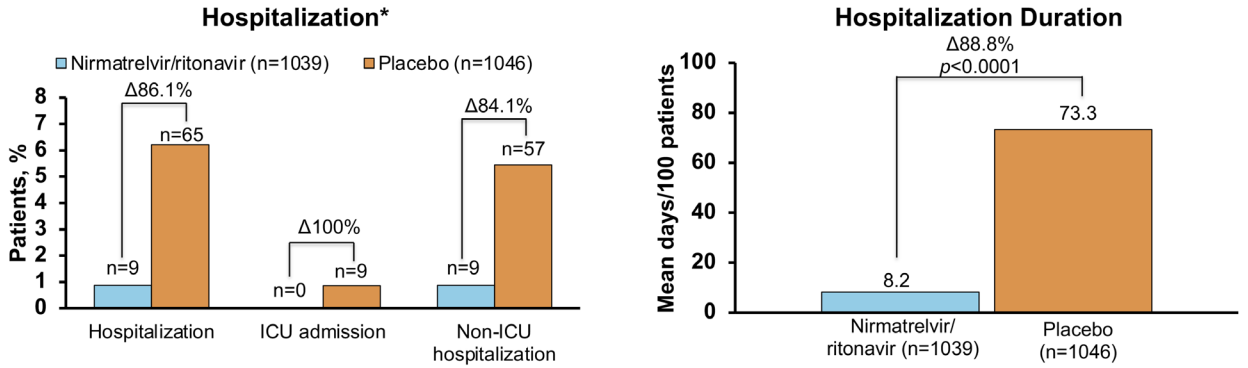
Hammond J et al. Sustained Alleviation and Resolution of Targeted COVID-19 Symptoms With Nirmatrelvir/Ritonavir Versus Placebo Presented at IDWeek 2022; October 19–23, 2022; Washington, DC, USA

786 - Effect of Nirmatrelvir/Ritonavir versus Placebo on COVID-19–Related Hospitalizations and Other Medical Visits

Jennifer Hammond, PhD, reported additional secondary endpoints from the EPIC-HR trial

- This presentation includes **additional reporting of secondary endpoints from EPIC-HR including mortality through Week 24 and overall COVID-19–related healthcare utilization**
- Analyses reported are from the modified intent-to-treat 1 (**mITT1**) population*
- **Results**: **no patients who received nirmatrelvir/ritonavir died through Week 24, compared with 15 deaths in the placebo group (100% RRR in all cause mortality through Week 24)**
- **Fewer hospitalizations were reported among those who received nirmatrelvir/ritonavir compared with placebo** (**Figure A**)
  - No patients in the nirmatrelvir/ritonavir group and nine patients in the placebo group were admitted to the ICU
  - Mean days of hospitalization per 100 patients was significantly reduced among nirmatrelvir/ritonavir treated patients

A. COVID-19–Related Hospitalization (mITT1)



*Had ≥1 postbaseline visit through Day 28, were treated within 5 days of COVID-19 symptom onset, and at baseline did not and were not expected to receive COVID-19 therapeutic mAb treatment.
ICU, intensive care unit; mAb, monoclonal antibody; RRR, relative risk reduction

Hammond J et al. Effect of Nirmatrelvir/Ritonavir versus Placebo on COVID-19–Related Hospitalizations and Other Medical Visits. Presented at IDWeek 2022; October 19–23, 2022; Washington, DC, USA

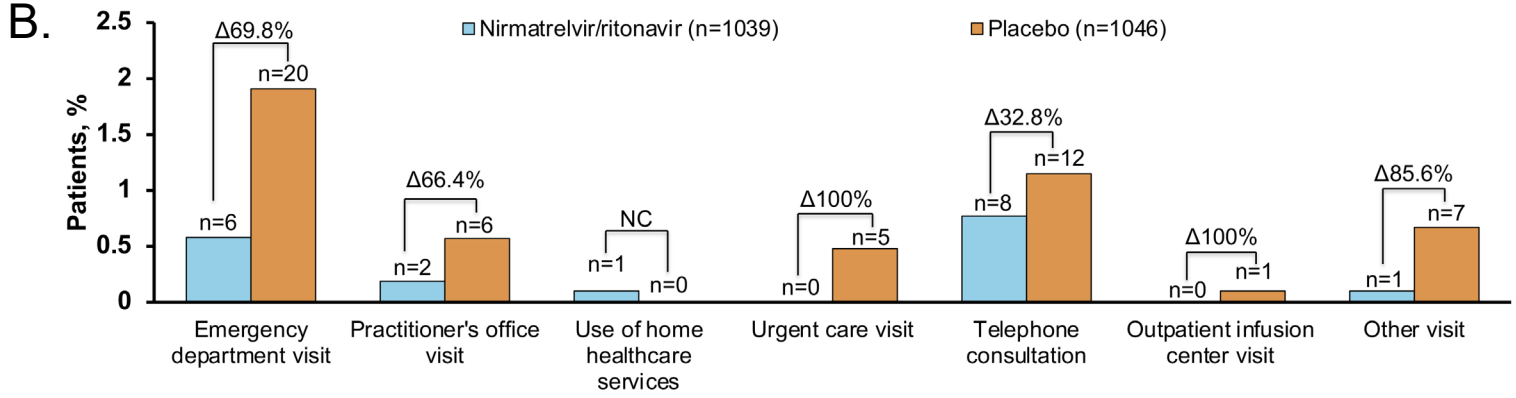
786 - Effect of Nirmatrelvir/Ritonavir versus Placebo on COVID-19–Related Hospitalizations and Other Medical Visits

Jennifer Hammond, PhD, reported additional secondary endpoints from the EPIC-HR trial

Key Messages

- **Results, continued:**
- **Through Day 34, fewer patients in the nirmatrelvir/ritonavir group reported COVID-19–related medical visits compared to placebo** (**Figure B**)
  - 2.2% (23/1039) with nirmatrelvir/ritonavir and 8.1% (85/1046) of patients who received placebo reported any COVID-19–related medical visit, corresponding to a 73% RRR ($p<0.0001$) with treatment

Other COVID-19–Related Medical Visits (mITT1)*



*Had ≥1 postbaseline visit through Day 28, were treated within 5 days of COVID-19 symptom onset, and at baseline did not and were not expected to receive COVID-19 therapeutic mAb treatment.
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Hammond J et al. Effect of Nirmatrelvir/Ritonavir versus Placebo on COVID-19–Related Hospitalizations and Other Medical Visits. Presented at IDWeek 2022; October 19–23, 2022; Washington, DC, USA

PAXLOVID® (Nirmatrelvir; Ritonavir) RWD

The following slides describe several real-world evidence studies conducted by third parties; they summarize sections of the studies, and should not be relied upon when making clinical decisions.

Pfizer did not sponsor and was not involved with any of these studies, including (without limitation) the design, execution, analysis or publication.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge

Ronen Arbel, Ph.D., Yael Wolff Sagy, Ph.D., Moshe Hoshen, Ph.D., Erez Battat, M.B.A., Gil Lavie, M.D., Ruslan Sergienko, M.A., Michael Friger, Ph.D., Jacob G. Waxman, M.D., Noa Dagan, M.D., Ran Balicer, M.D., Yatir Ben-Shlomo, B.Sc., Alon Peretz, M.D., Shlomit Yaron, M.D., Danielle Serby, M.Sc., Ariel Hammerman, Ph.D., and Doron Netzer, M.D.

Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 — United States, April–September 2022

Early Release / November 22, 2022 / 71

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Clinical Infectious Diseases

MAJOR ARTICLE

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Oral Nirmatrelvir and Ritonavir in Nonhospitalized Vaccinated Patients With Coronavirus Disease 2019 (COVID-19)

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Clinical Infectious Diseases

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Real-World Effectiveness of Nirmatrelvir/Ritonavir on Coronavirus Disease 2019 (COVID-19)–Associated Hospitalization Prevention: A Population-based Cohort Study in the Province of Quebec, Canada

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Effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system

Joseph A Lewnard, John M McLaughlin, Debbie Malden, Vennis Hong, Laura Puzniak, Bradley K Ackerson, Bruno J Lewin, Jeniffer S Kim, Sally F Shaw, Harpreet Takhar, Luis Jodar, Sara Y Tartof

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Effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system

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Summary

Background In the USA, oral nirmatrelvir–ritonavir is authorised for use in patients aged 12 years or older with mild-to-moderate COVID-19 who are at risk of progression to severe disease and hospitalisation. We aimed to establish the effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and death in people with COVID-19 in an outpatient prescribing context in the USA.

Methods In this matched observational outpatient cohort study in the Kaiser Permanente Southern California (CA, USA) health-care system, data were extracted from electronic health records of non-hospitalised patients aged 12 years or older who received a positive SARS-CoV-2 PCR test result (their index test) between April 8 and Oct 7, 2022, and had not received another positive test result within the preceding 90 days. We compared outcomes between people who received nirmatrelvir–ritonavir and those who did not receive nirmatrelvir–ritonavir by matching cases by date, age, sex, clinical status (including care received, the presence or absence of acute COVID-19 symptoms at testing, and time from symptom onset to testing), vaccination history, comorbidities, health-care seeking during the previous year, and BMI. Our primary endpoint was the estimated effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions or death within 30 days of a positive test for SARS-CoV-2.

Findings 7274 nirmatrelvir–ritonavir recipients and 126 152 non-recipients with positive SARS-CoV-2 tests were included in our study. 5472 (75·2%) treatment recipients and 84 657 (67·1%) non-recipients were tested within 5 days of symptom onset. Nirmatrelvir–ritonavir had an overall estimated effectiveness of 53·6% (95% CI 6·6–77·0) in preventing hospital admission or death within 30 days of a positive test for SARS-CoV-2, which increased to 79·6% (33·9–93·8) when nirmatrelvir–ritonavir was dispensed within 5 days of symptom onset. Within the subgroup of patients tested within 5 days of symptom onset and whose treatment was dispensed on the day of their test, the estimated effectiveness of nirmatrelvir–ritonavir was 89·6% (50·2–97·8).

Interpretation In a setting with high levels of COVID-19 vaccine uptake, nirmatrelvir–ritonavir effectively reduced the risk of hospital admission or death within 30 days of a positive outpatient SARS-CoV-2 test.

Lewnard JA. et al. 2023. Effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system. Lancet Infect Dis. 2023 Mar 15; S1473-3099(23)00118-4.

*Nirmatrelvir/ ritonavir en la Union Europea no dispone de autorización en niños

PAXLOVID reduce el riesgo de hospitalización o muerte a los 30 días

Effectiveness of PAXLOVID in preventing progression to severe disease endpoints

	Discordant sets		Estimated effectiveness (95% CI)	*P* value (two-sided)
	Outcome observed for recipient, non-recipient censored (n)	Outcome observed for non-recipient, recipient censored (n)		
All-cause hospital admission or death (within 30 days of positive SARS-CoV-2 test)				
Within 5 days of symptom onset	8	11	79.6% (33.9–93.8)	0.0080
Any time (regardless of symptoms)	26	23	53.6% (6.6–77.0)	0.031
All-cause ICU admission, mechanical ventilation, or death (within 60 days of positive SARS-CoV-2 test)				
Within 5 days of symptom onset	2	7	89.2% (-25.0–99.3)	0.075
Any time (regardless of symptoms)	10	11	84.1% (18.8–96.9)	0.027

Receipt of nirmatrelvir–ritonavir **within 5 days of symptom onset** had an estimated effectiveness of **79.6%** (95% CI 33.9–93.8; *P*=0.0080) against progression to hospital admission or death due to any cause within 30 days.

CI, confidence interval; ICU, intensive care unit.

Lewnard JA. et al. 2023. Effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system. Lancet Infect Dis. 2023 Mar 15; S1473-3099(23)00118-4.

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JAMA Internal Medicine | Original Investigation

Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition

Yan Xie, PhD; Taeyoung Choi, MPH; Ziyad Al-Aly, MD

IMPORTANCE Post–COVID-19 condition (PCC), also known as long COVID, affects many individuals. Prevention of PCC is an urgent public health priority.

OBJECTIVE To examine whether treatment with nirmatrelvir in the acute phase of COVID-19 is associated with reduced risk of PCC.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used the health care databases of the US Department of Veterans Affairs (VA) to identify patients who had a SARS-CoV-2 positive test result between January 3, 2022, and December 31, 2022, who were not hospitalized on the day of the positive test result, who had at least 1 risk factor for progression to severe COVID-19 illness, and who had survived the first 30 days after SARS-CoV-2 diagnosis. Those who were treated with oral nirmatrelvir within 5 days after the positive test (n = 35 717) and those who received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection (control group, n = 246 076) were identified.

EXPOSURES Treatment with nirmatrelvir or receipt of no COVID-19 antiviral or antibody treatment based on prescription records.

MAIN OUTCOMES AND MEASURES Inverse probability weighted survival models were used to estimate the association of nirmatrelvir (vs control) with post-acute death, post-acute hospitalization, and a prespecified panel of 13 post-acute COVID-19 sequelae (components of PCC) and reported in relative scale as relative risk (RR) or hazard ratio (HR) and in absolute scale as absolute risk reduction in percentage at 180 days (ARR).

Editor's Note

Supplemental content

RESULTS A total of 281 793 patients (mean [SD] age, 61.99 [14.96]; 242 383 [86.01%] male) who had a positive SARS-CoV-2 test result and had at least 1 risk factor for progression to severe COVID-19 illness were studied. Among them, 246 076 received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection, and 35 717 received oral nirmatrelvir within 5 days after the positive SARS-CoV-2 test result. Compared with the control group, nirmatrelvir was associated with reduced risk of PCC (RR, 0.74; 95% CI, 0.72-0.77; ARR, 4.51%; 95% CI, 4.01-4.99), including reduced risk of 10 of 13 post-acute sequelae (components of PCC) in the cardiovascular system (dysrhythmia and ischemic heart disease), coagulation and hematologic disorders (pulmonary embolism and deep vein thrombosis), fatigue and malaise, acute kidney disease, muscle pain, neurologic system (neurocognitive impairment and dysautonomia), and shortness of breath. Nirmatrelvir was also associated with reduced risk of post-acute death (HR, 0.53; 95% CI, 0.46-0.61); ARR, 0.65%; 95% CI, 0.54-0.77), and post-acute hospitalization (HR, 0.76; 95% CI, 0.73-0.80; ARR, 1.72%; 95% CI, 1.42-2.01). Nirmatrelvir was associated with reduced risk of PCC in people who were unvaccinated, vaccinated, and boosted, and in people with primary SARS-CoV-2 infection and reinfection.

CONCLUSIONS AND RELEVANCE This cohort study found that in people with SARS-CoV-2 infection who had at least 1 risk factor for progression to severe disease, treatment with nirmatrelvir within 5 days of a positive SARS-CoV-2 test result was associated with reduced risk of PCC across the risk spectrum in this cohort and regardless of vaccination status and history of prior infection; the totality of findings suggests that treatment with nirmatrelvir during the acute phase of COVID-19 may reduce the risk of post-acute adverse health outcomes.

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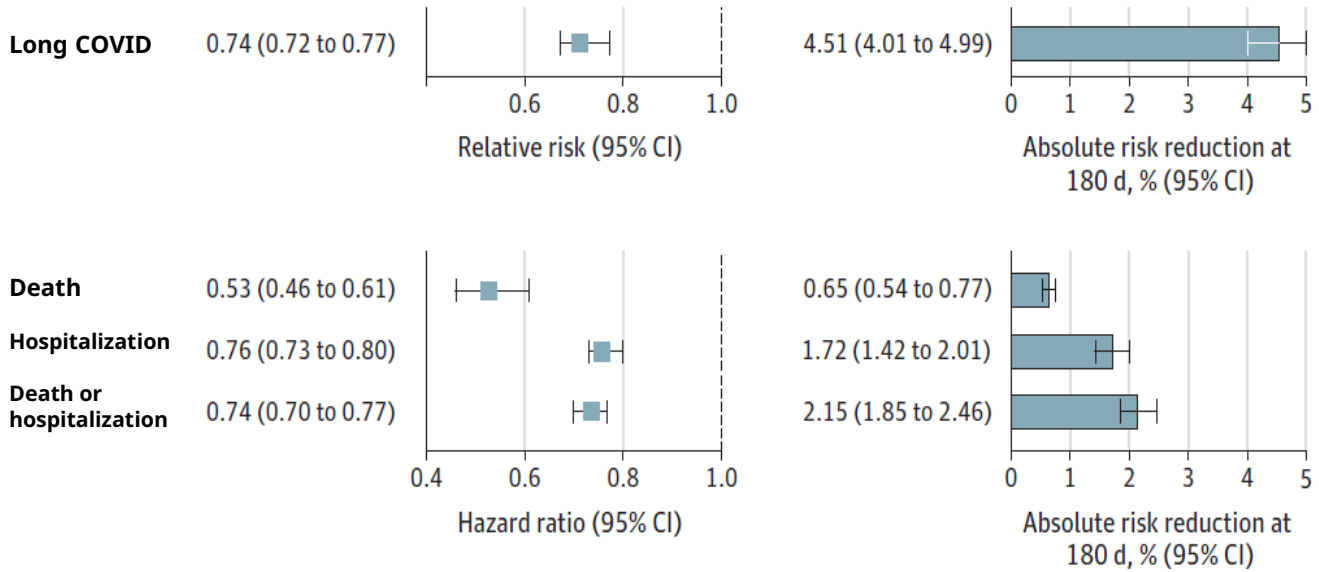
Nirmatrelvir y las secuelas post–agudas del long COVID

US, cohort study (Department of Veterans Affairs), 3 January–31 December 2022

Risk reduction of outcomes with nirmatrelvir (n=35,717) vs no-treatment control group (n=246,076)*



Among patients with SARS-CoV-2 infection and ≥1 risk factor for progression to severe illness,† treatment with nirmatrelvir within 5 days of a positive SARS-CoV-2 test reduced the risk of long COVID by 26%, post-acute death by 47%, and post–acute hospitalization by 24% compared with no treatment.

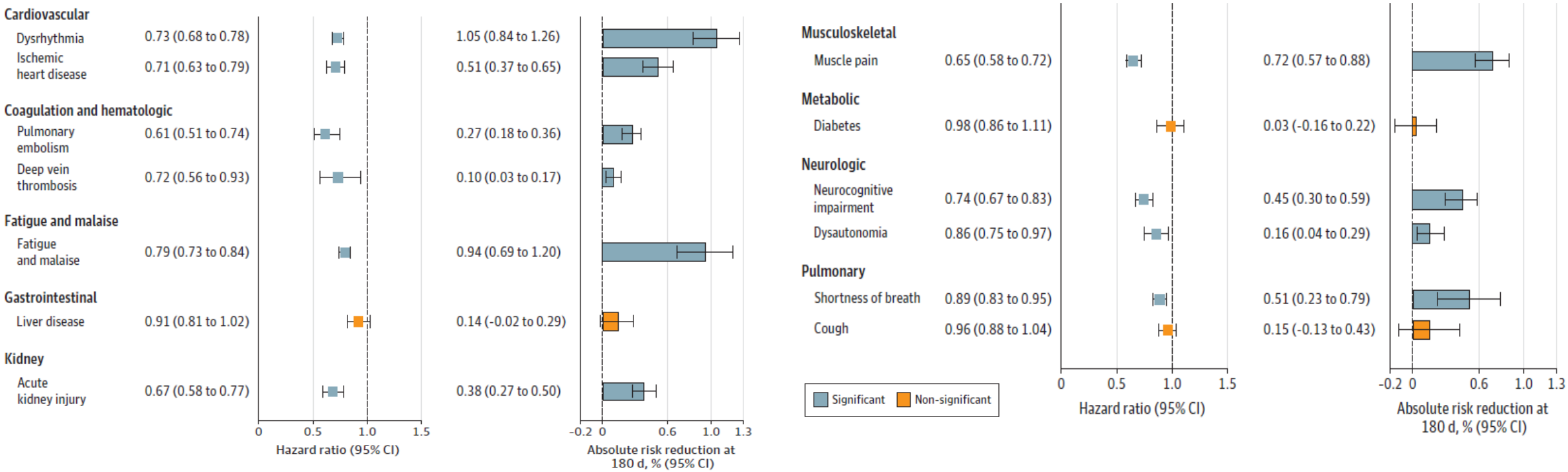
*Outcomes were ascertained 30 days after the SARS-CoV-2 positive test result until the end of follow-up. Adjusted hazard ratios and 95% CIs are presented. Absolute risk reduction of nirmatrelvir compared with the control group per 100 persons at 180 days and associated 95% CIs were estimated based on the difference of survival probability in the nirmatrelvir group compared with the control group.
†Risk factors included being older than 60 years, a BMI of >25, current smoker, cancer, cardiovascular disease, kidney disease, chronic lung disease, diabetes, immune dysfunction, and hypertension.
BMI=body mass index; d=days.

Xie Y, et al. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition. JAMA Intern Med. Published online 23 March 2023. doi:10.1001/jamainternmed.2023.0743

Nirmatrelvir/ ritonavir no tiene indicación aprobada para el tratamiento de long COVID. Esta información se presenta como respuesta a la solicitud expresa del profesional sanitario

Nirmatrelvir y las secuelas post–agudas del long COVID

Risk reduction for individual post–acute sequelae with nirmatrelvir (n=35,717) vs no-treatment control group (n=246,076)*



Compared with no treatment, nirmatrelvir was associated with reduced risk of 10 of the 13 prespecified post–acute sequelae evaluated, including sequelae in the cardiovascular system, coagulation and hematologic disorders, fatigue and malaise, liver disease, acute kidney disease, muscle pain, neurologic system, and shortness of breath.

*Outcomes were ascertained 30 days after the SARS-CoV-2 positive test result until the end of follow-up. Adjusted hazard ratios and 95% CIs are presented. Absolute risk reduction of nirmatrelvir compared with the control group per 100 persons at 180 days and associated 95% CIs were estimated based on the difference of survival probability in the nirmatrelvir group compared with the control group.

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PAXLOVID® (Nirmatrelvir; Ritonavir): Información Relevante Ficha Técnica

▼Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Paxlovid: Indicación terapéutica y Posología

Paxlovid está indicado para el tratamiento de la enfermedad por coronavirus 2019 (COVID 19) en adultos (18 años de edad y mayores) que no requieren aporte de oxígeno suplementario y que tienen un riesgo alto de progresar a COVID 19 grave

- **300 mg de nirmatrelvir (dos comprimidos de color rosa de 150 mg) con 100 mg de ritonavir (un comprimido de color blanco de 100 mg), tomados todos juntos cada 12 horas durante 5 días.**
- Paxlovid se debe administrar lo antes posible tras el diagnóstico de COVID-19 y dentro de los 5 días posteriores al inicio de los síntomas
- **Si el paciente olvida una dosis** de Paxlovid y está dentro de las 8 horas posteriores a la hora en que lo toma normalmente, el paciente debe tomarla lo antes posible y reanudar la pauta posológica normal. Si el paciente olvida una dosis y han pasado más de 8 horas, el paciente no debe tomar la dosis olvidada y, en su lugar, debe tomar la siguiente dosis a la hora programada habitual. El paciente no debe tomar una dosis doble para compensar la dosis olvidada.
- Paxlovid se puede tomar **con o sin alimentos**. Los comprimidos se deben tragar enteros y **no se deben masticar, partir ni triturar**, ya que no hay datos disponibles actualmente.

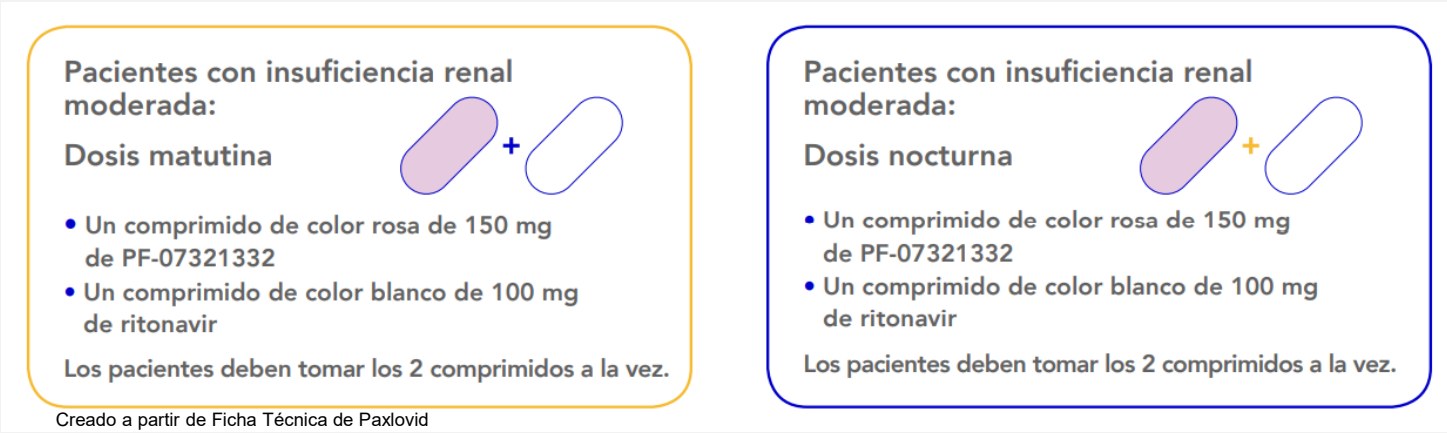
Creado a partir de Ficha Técnica de Paxlovid

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Poblaciones especiales

Insuficiencia renal

- **Insuficiencia renal leve** (eGRF ≥ 60 ml/min a <90 ml/min): **no es necesario ajustar la dosis**.
- **Insuficiencia renal moderada** (eGRF ≥ 30 a <60 ml/min): la dosis de Paxlovid se debe reducir a nirmatrelvir/ritonavir 150 mg/100 mg cada 12 horas durante 5 días (**sólo tienen que tomar un comprimido de color rosa de nirmatrelvir con 1 comprimido de color blanco de ritonavir cada 12 horas**).



Creado a partir de Ficha Técnica de Paxlovid

- **Insuficiencia renal grave** (eGRF <30 ml/min, incluyendo pacientes con una insuficiencia renal en fase terminal sometidos a hemodiálisis): Paxlovid **no debe de ser utilizado**.
  No hay datos clínicos disponibles en pacientes con insuficiencia renal grave (incluidos pacientes con ESRD). En base a los datos farmacocinéticos (ver sección 5.2), **el uso de Paxlovid en pacientes con insuficiencia renal grave podría dar lugar a una sobreexposición con una potencial toxicidad.**

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Poblaciones especiales

Insuficiencia hepática

- **Insuficiencia hepática leve** (Child-Pugh Clase A) **o moderada** (Child-Pugh Clase B): **No es necesario ajustar la dosis** de Paxlovid
- **Insuficiencia hepática grave**: No se recomienda Paxlovid en pacientes con insuficiencia hepática grave. Paxlovid no debe ser utilizado en pacientes con insuficiencia hepática grave (Child-Pugh Clase C)

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Poblaciones especiales

Mujeres en edad fértil	No existen datos sobre el uso de Paxlovid en mujeres embarazadas que permitan dar información sobre el riesgo de presentar problemas en el desarrollo relacionados con el medicamento; las mujeres en edad fértil deben evitar quedarse embarazadas durante el tratamiento con Paxlovid y, como medida de precaución, hasta 7 días después de finalizar el tratamiento con Paxlovid.
Fertilidad	No hay datos en humanos sobre el efecto de Paxlovid (nirmatrelvir y ritonavir) ni ritonavir sólo en la fertilidad. Ni Nirmatrelvir ni ritonavir, evaluados separadamente, causaron efectos sobre la fertilidad en ratas.
Embarazo	Hay datos limitados relativos el uso de Paxlovid en mujeres embarazadas. No se recomienda Paxlovid durante el embarazo y en mujeres en edad fértil que no utilicen métodos anticonceptivos a menos que su condición clínica requiera tratamiento con Paxlovid.
Lactancia	Debe interrumpirse la lactancia durante el tratamiento con Paxlovid y, como medida de precaución, hasta 7 días después de finalizar el tratamiento con Paxlovid.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Reacciones adversas

Resumen del perfil de seguridad

- Las reacciones adversas más comunes notificadas durante el tratamiento con Paxlovid (nirmatrelvir /ritonavir 300 mg/100 mg) cada 12 horas durante 5 días y durante 34 días tras la última dosis fueron disgeusia (5,6 %), diarrea (3,1 %), cefalea (1,4 %) y vómitos (1,1 %).

Las reacciones adversas de la tabla 2 se enumeran a continuación según la clasificación por órganos y sistemas y por frecuencia. Las frecuencias se definen de la siguiente manera: Muy frecuentes (≥ 1/10), frecuentes (≥ 1/100 a < 1/10), poco frecuentes (≥ 1/1.000 a < 1/100), raras (≥ 1/10.000 a < 1/1.000), frecuencia no conocida (no puede estimarse a partir de los datos disponibles).

Tabla 2: Reacciones adversas con Paxlovid

Clasificación por órganos y sistemas	Categoría de frecuencia	Reacciones adversas
Trastornos del sistema inmunológico	Poco frecuentes	Hipersensibilidad incluyendo prurito y erupción
	Raros	Anafilaxia
Trastornos del sistema nervioso	Frecuentes	Disgeusia, cefalea
Trastornos gastrointestinales	Frecuentes Poco frecuentes	Diarrea, vómitos, náuseas Dolor abdominal
Trastornos generales y alteraciones en el lugar de administración	Raros	Malestar

Notificación de sospechas de reacciones adversas

Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: www.notificaRAM .es

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Reacciones adversas

Reacciones de hipersensibilidad

Se han notificado anafilaxia y otras reacciones de hipersensibilidad con Paxlovid (ver sección 4.8). Se han notificado casos de necrólisis epidérmica tóxica y síndrome de Stevens-Johnson con ritonavir, un componente de Paxlovid (consulte la ficha técnica de Norvir). Si se producen signos y síntomas de una reacción de hipersensibilidad o anafilaxia clínicamente significativos, interrumpa inmediatamente el tratamiento con Paxlovid e inicie el tratamiento con los medicamentos adecuados o el tratamiento de apoyo.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Advertencias y precauciones especiales de empleo

Riesgo de reacciones adversas graves debido a interacciones con otros medicamentos

El manejo de las interacciones farmacológicas (DDIs, por sus siglas en inglés) en pacientes con COVID-19 de alto riesgo que reciben múltiples medicamentos concomitantes puede ser compleja y requiere una comprensión profunda de la naturaleza y la magnitud de la interacción con todos los medicamentos concomitantes. En ciertos pacientes, se debe considerar un enfoque multidisciplinar (p. ej., en el que participen médicos y especialistas en farmacología clínica) para el manejo de las DDIs, especialmente si se suspenden los medicamentos concomitantes, se reduce su dosis o si es necesario vigilar los efectos secundarios.

Efectos de Paxlovid sobre otros medicamentos

- **El inicio del tratamiento con Paxlovid**, un inhibidor del CYP3A, **en pacientes que reciben medicamentos metabolizados por el CYP3A o el inicio del tratamiento con medicamentos metabolizados por el CYP3A** en pacientes que ya reciben Paxlovid puede aumentar las concentraciones plasmáticas de medicamentos metabolizados por el CYP3A (ver sección 4.5).

Efectos de otros medicamentos sobre Paxlovid

- **El inicio del tratamiento con medicamentos que inhiben o inducen el CYP3A** puede aumentar o disminuir las concentraciones de Paxlovid, respectivamente.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Advertencias y precauciones especiales de empleo

Riesgo de reacciones adversas graves debido a interacciones con otros medicamentos

- Estas interacciones **pueden dar lugar a**:
  - Reacciones adversas clínicamente significativas, que pueden dar lugar a acontecimientos graves, potencialmente mortales o mortales debido a una mayor exposición a medicamentos concomitantes.
  - Reacciones adversas clínicamente significativas derivadas de una mayor exposición a Paxlovid.
  - Pérdida del efecto terapéutico de Paxlovid y posible aparición de resistencia viral.

- **Ver la tabla 1 de la Ficha Técnica** para consultar los medicamentos que están contraindicados para su uso concomitante con nirmatrelvir/ritonavir y para consultar las interacciones potencialmente significativas con otros medicamentos (ver sección 4.5).
- **Se debe considerar las interacciones potenciales con otros medicamentos antes y durante el tratamiento con Paxlovid**; se deben revisar los medicamentos concomitantes durante el tratamiento con Paxlovid y se debe monitorizar al paciente para detectar cualquier reacción adversa relacionada con los medicamentos concomitantes.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

Contraindicaciones

Medicamentos cuyo aclaramiento depende en gran medida del CYP3A y cuyas concentraciones elevadas se relacionan con reacciones graves o potencialmente mortales.

- Antagonista del receptor adrenérgico Alpha$_1$: alfuzosina.
- Antianginoso: ranolazina.
- Antiarrítmicos: amiodarona, dronedarona, flecainida, propafenona, quinidina.
- Antibióticos: ácido fusídico.
- Antineoplásicos: neratinib, venetoclax.
- Medicamentos para la gota: colchicina.
- Antihistamínicos: terfenadina.
- Antipsicóticos/neurolépticos: clozapina, lurasidona, pimozida, quetiapina.
- Medicamentos para la hiperplasia benigna de próstata: silodosina.
- Medicamentos cardiovasculares: eplerenona, ivabradina.
- Derivados ergóticos: dihidroergotamina, ergonovina, ergotamina, metilergonovina.
- Agentes para la motilidad gastrointestinal: cisaprida.
- Inmunosupresores: voclosporina.
- Agentes modificadores de lípidos:
  - Inhibidores de la HMG-Co-A reductasa: lovastatina, simvastatina.
  - Inhibidor de la proteína de transferencia microsomal de triglicéridos (PTMT): lomitapida.
- Medicamentos para la migraña: eletriptán.
- Inhibidores de la PDE5: avanafilo, sildenafilo, tadalafilo, vardenafilo.
- Sedantes/somníferos: clorazepato, diazepam, estazolam, flurazepam, midazolam oral y triazolam.
- Antagonistas de los receptores de vasopresina: tolvaptán.

Medicamentos que son inductores potentes del CYP3A, en los que una reducción significativa en las concentraciones plasmáticas de nirmatrelvir/ritonavir puede estar relacionada con la pérdida potencial de la respuesta virológica y con una posible resistencia.

- Antibióticos: rifampicina.
- Antineoplásicos: apalutamida.
- Anticonvulsivos: carbamazepina, fenobarbital, fenitoína.
- Productos de fitoterapia: hierba de san Juan (*Hyperycum perforatum*).

No se puede comenzar el tratamiento con Paxlovid inmediatamente después de la interrupción del tratamiento con inductores del CYP3A4 debido al retraso en la compensación del inductor del CYP3A recién interrumpido (ver sección 4.5).

Se debe considerar un enfoque multidisciplinar (p. ej., en el que participen médicos y especialistas en farmacología clínica) para determinar el momento adecuado para el inicio del tratamiento con Paxlovid teniendo en cuenta el retraso en la compensación del inductor del CYP3A recién interrumpido y la necesidad de iniciar el tratamiento con Paxlovid dentro de los 5 días posteriores al inicio de los síntomas.

Se debe considerar un enfoque multidisciplinar (p. ej., en el que participen médicos y especialistas en farmacología clínica) para determinar el momento adecuado para el inicio del tratamiento con Paxlovid teniendo en cuenta el retraso en la compensación del inductor del CYP3A recién interrumpido y la necesidad de iniciar el tratamiento con Paxlovid dentro de los 5 días posteriores al inicio de los síntomas.

Ficha Técnica Paxlovid. Paxlovid, INN-Nirmatrelvir + ritonavir (aemps.es). Acceso Mayo 2023

EPIC-HR: interacciones con otros medicamentos

- The **concomitant use of nirmatrelvir plus ritonavir and certain drugs may result in potentially important drug interactions**

- Such **interactions need to be managed through**:
  - **Dose reduction of the concomitant medication**
  - **Use of an alternative concomitant medication**
  - **Increased monitoring for adverse events or concomitant medication drug levels**
  - **Temporary discontinuation of concomitant medications**
  - **Avoidance of coadministration**

- **Drug interactions with low-dose ritonavir (100 mg) given over a short duration of 5 days for treatment of COVID-19 are likely to be of lesser clinical consequence than long-term use of low-dose or standard-dose (600 mg) ritonavir for patients with human immunodeficiency virus**

- **Nirmatrelvir plus ritonavir is contraindicated with use of certain drugs because of the risk of serious adverse events**

Hammond J et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. Covid-19 N Engl J Med 2022 Apr 14;386(15):1397-1408. doi: 10.1056/NEJMoa2118542

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WHO updates COVID-19 guidelines on masks, treatments and patient care

13 January 2023 | News release | Reading time: 2 min (548 words)

Review of COVID-19 treatments

WHO has extended its strong recommendation for the use of nirmatrelvir-ritonavir (also known by its brand name 'Paxlovid').

Pregnant or breastfeeding women with non-severe COVID-19 should consult with their doctor to determine whether they should take this drug, due to 'likely benefits' and a lack of adverse events having been reported.

Nirmatrelvir-ritonavir was first recommended by WHO in April 2022. WHO strongly recommends its use in mild or moderate COVID-19 patients who are at high-risk of hospitalization. In December 2022, the first generic producer of the drug was prequalified by WHO.

WHO also reviewed the evidence on two other medicines, sotrovimab and casirivimab-imdevimab, and maintains strong recommendations against their use for treating COVID-19. These monoclonal antibody medicines lack or have diminished activity against the current circulating virus variants.

There are currently 6 proven treatment options for patients with COVID-19, three that prevent hospitalization in high-risk persons and three that save lives in those with severe or critical disease. Except for corticosteroids, access to other drugs remains unsatisfactory globally.

Disponible en: WHO updates COVID-19 guidelines on masks, treatments and patient care. Acceso Mayo 2023

MUCHAS GRACIAS

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