Application for Inclusion of Nirmatrelvir-Ritonavir to the World Health Organization's Model Lists of Essential Medicines and Essential Medicines for Children

1 Summary statement of the proposal for inclusion

Cumulative cases of Covid-19 are over 642 million, with 6.6 million global deaths.[1] Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable. There remains a need for more effective treatments for COVID-19.

WHO guidance makes a strong recommendation for the use of nirmatrelvir-ritonavir for patients with non-severe Covid-19 at highest risk of hospitalization. This is based on a reduction in hospitalization amongst patients at highest risk of 51 per 1000 patients treated, with moderate certainty of evidence. This evidence derives from prospective meta-analysis which is the basis of all of the WHO Therapeutics and COVID-19 Living Guidelines; these are summarised in the application. Evidence supports the safety and tolerability of nirmatrelvir-ritonavir, with separate meta-analysis suggesting that nirmatrelvir-ritonavir decreases discontinuation of study drug due to adverse events compared with placebo (RR 0.49, 95% CI 0.30 to 0.80, moderate-certainty evidence). Although there are a number of therapeutic options for non-severe Covid-19, the guideline group concluded that:

> *…nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives, has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies.*

These guidelines support global use of the medicine, and highlight its preferred status.[2] This application will ensure that the Essential Medicines List reflects current evidence-based guidance, and supports international work through the ACT-Accelerator to make effective therapies available in an equitable and transparent manner.[3]

The application relates to both the Model List of Essential Medicines and the Essential Medicines for Children (although only to be used in those over 12 years old).

2 Relevant WHO technical department and focal point

Janet Diaz, Clinical Management Unit, Country Readiness Strengthening, HQ.

3 Name of organisation(s) consulted and/or supporting the application

The WHO Guideline Development Group for Covid-19 therapeutics has developed and published recommendations on the use of this medicine.[2]

4 International names for medicine within this application

4.1 International non-proprietary name (INN)

- nirmatrelvir
- ritonavir

4.2 Anatomical Therapeutic Chemical code (ATC)

J05AE30

5 Dose

The recommended dose of nirmatrelvir-ritonavir in Covid-19 is 300 mg (two 150 mg tablets) of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days. This applies to adults and for children aged 12 years and older. Below 12 years, use is not recommended.

No dose adjustment is needed in patients with mild renal impairment. In moderate renal insufficiency (GFR 30–59 mL/min) the dose reduction is 150 mg of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days.[4]

No dosage adjustment of nirmatrelvir is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.[4]

6 Whether listing is requested as an individual medicine or as representative of a pharmacological class

This application is for listing as an individual medicine.

7 Treatment details

7.1 Requirements for diagnosis

The medication should ideally be administered within five days of symptom onset. Diagnostic possibilities include rapid diagnostic tests (RDT) and polymerase chain reaction (PCR), both of which are supplied by multiple manufacturers. There is no stated preference for diagnostic approach within the guidance, although it is noted that:

> *…availability and use of appropriate SARS-CoV-2 diagnostic tests is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of rapid diagnostic tests such as antigen-detection assays can improve early diagnosis in the community and in primary health care settings. Health care systems must, however, gain expertise in choosing and implementing rapid tests, choosing those most applicable to their settings.*

7.2 Requirements for treatment and monitoring

Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days. There is no stipulated monitoring regimen.

8 Mechanism of action

Nirmatrelvir inhibits the SARS-CoV-2 protease (3CLpro), thereby preventing cleavage of the viral polyprotein which is needed for viral proteins to become functional.[5] Inhibition of the protease renders the virus unable to replicate. Nirmatrelvir is co-administered with ritonavir, a HIV protease inhibitor, used in this context to boost the pharmacokinetics of nirmatrelvir but without exerting any direct antiviral activity itself.[6] Therefore, the combination should be considered as antiviral monotherapy. Nirmatrelvir was developed as an orally deliverable analogue of an intravenous prodrug (lufotrelvir; PF-07304814). The drug was originally developed for SARS-CoV, and has been subsequently repurposed for SARS-CoV-2.

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 in differentiated normal human bronchial epithelial cells with an EC50 of 0.06 micromolar and an EC90 of 0.18 micromolar [30]. In healthy volunteers, plasma maximum concentrations of nirmatrelvir were 2210 ng/mL with a half-life of 6 hours following a 300/100 mg dose of nimatrelvir-ritonavir, and steady-state pharmacokinetics were achieved on day 2 (an EC90 of 0.18 micromolar

equates to approximately 90 ng/mL).[7] High doses (300 mg/kg) of unboosted nimatrelvir was active against murine-adapted SARS-CoV-2 in mice but with maximum concentrations higher than those achieved at 300/100 mg doses in healthy human volunteers.[6] High doses (250 mg/kg) of unboosted nimatrelvir also had efficacy in SARS-CoV-2-infected Syrian golden hamsters but no pharmacokinetic data are available in this species.[8] Based upon genome sequence of Omicron, there appears to be no molecular basis for a loss of activity. Nimatrelvir retains activity against BA.1 Omicron in vitro[9] but in vivo data are currently unavailable.

Much more data are required to ascertain the rate at which resistance will emerge for nirmatrelvir. Single amino acid changes introduced into the protease sequence can reduce activity of nirmatrelvir by between 23.6- and 39-fold. Mouse hepatitis virus (used as a betacoronavirus surrogate) acquired several mutations under a selective pressure in vitro, and these reduced nirmatrelvir activity by between 4- and 91-fold.[7] Two amino substitutions were described in clinical trials, one of which did not impact nirmatrelvir activity.

Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions that will require careful consideration. Short durations of therapy needed in COVID-19 may make drug interactions easier to manage than they are for HIV, but twice daily administration means that the ritonavir dose is double that used in most modern antiretroviral regimens. The impact of ritonavir on metabolism may also outlast dosing by several days.

9 Review of benefits (summary of evidence of comparative effectiveness)

Recommendations concerning nirmatrelvir-ritonavir for patients with non-severe COVID-19 were published on 22 April 2022 as the tenth version of the WHO living guideline. It follows the availability of two RCTs within a network analysis, with the following PICO:

Table 1 – PICO used in systematic review informing use of nirmatrelvir-ritonavir for non-severe COVID-19

Population	Patients with non-severe confirmed COVID-19 (according to WHO definitions)
Intervention	Nirmatrelvir/ritonavir + usual care
Comparator	Usual care
Outcomes	See outcome prioritization
Subgroups for relative effects	Children vs adults vs. older people Time from symptom onset Serological status Disease severity
Subgroups for absolute effects	Age and chronic conditions Serological status Vaccination status
Co-intervention at baseline	Monoclonal antibodies, molnupiravir, remdesivir

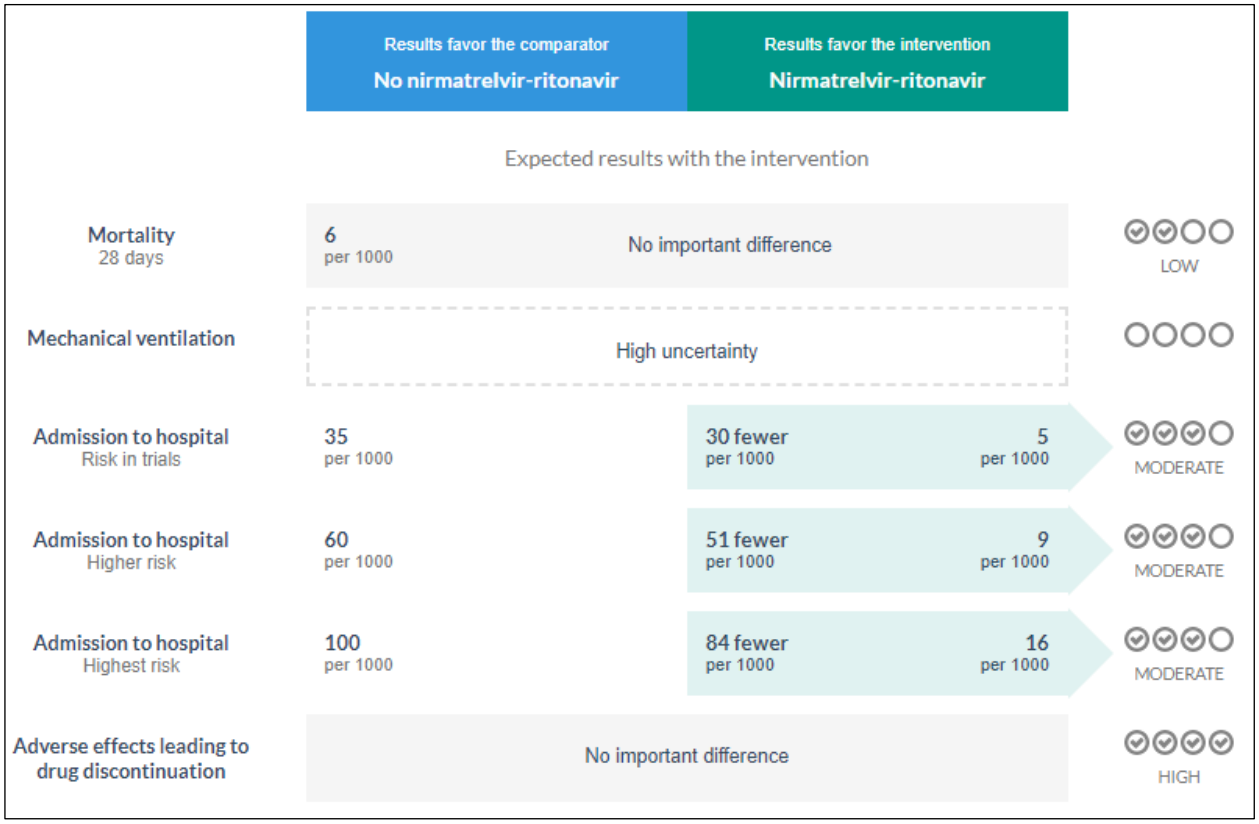
The evidence summary on nirmatrelvir-ritonavir was informed by two trials (EPIC-SR and EPIC-HR) with 3100 participants included in the meta-analysis, see Table 2.[10,11]

Table 2 – Studies included in the WHO Living Guidelines meta-analysis

Study	Publication status	Location	Median age	Percent male	Severity	Dose	N
EPIC-SR NCT05011513	Not published, ongoing (interim data)	Multi-continental	NA		All non-severe	Nirmatrelvir 300 mg and ritonavir 100 mg twice daily for 5 days	673
EPIC-HR NCT04960202	Not published (completed	Multi-continental	46	51	All non-severe	Nirmatrelvir 300 mg and ritonavir 100 mg twice daily for 5 days	2246

For hospital admission at 28 days, odds ratio 0.15 (CI 95% 0.06 - 0.38) for nirmatrelvir vs no nirmatrelvir, based on data from 3078 participants. Absolute rates were 5 per 1000 and 35 per 1000 patients respectively. The difference is 30 fewer admissions per 1000 patients (95%CI 33 fewer to 21 fewer). As can be seen in Figure 1, this was modelled for both the trial populations, and for those at higher baseline risk. Subgroup analysis by age and serologic status were not significantly different.

Figure 1 – Graphical evidence summary of the benefit of nirmatrelvir-ritonavir for non-severe Covid-19[2]



Higher risk individuals are those of older age (> 60 years), those with immunosuppression and/or chronic disease, and those unvaccinated against COVID-19. The interpretations forming the recommendation[2] are given below:

> *In highest risk patients in whom an appreciable decrease in hospitalization with nirmatrelvir-ritonavir is likely, the benefits clearly outweigh the harms, thus warranting the strong recommendation in favour of the drug.*
>
> *In patients with non-severe COVID-19, nirmatrelvir-ritonavir likely reduces admission to hospital (moderate certainty evidence). It may have little or no impact on mortality (low certainty evidence). There are no data reported for time to symptom resolution or mechanical ventilation.*

9.1 Certainty of evidence

Certainty of evidence was rated as: moderate for decreased hospitalization (rated down due to concerns regarding imprecision and risk of bias); low for mortality (rated down due to serious imprecision and indirectness) and high for adverse effects leading to drug discontinuation.

Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represent the major source of indirectness for which the GDG rated down the certainty of the evidence.[12]

Whilst there are a number of available therapeutic options amongst this patient population, of note, the WHO guidelines conclude that "*nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives, has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies*", which represents advantages in safety and pragmatic use.

10 Review of harms and toxicity (summary of evidence of safety)

The WHO living guidelines (v12) provided a systematic summary of available evidence.[2] Within the systematic review, adverse events leading to drug discontinuation (n=2246 patients) occurred in the placebo group at 4.2%, and in the nirmatrelvir group at 2.1% suggesting safety in a trial setting. The interpretation, in the context of use in Covid-19, was given as:

> *Treatment does not increase the likelihood of adverse effects leading to drug discontinuation (high certainty evidence), though diarrhoea and dysgeusia (loss of taste) have occurred more frequently with nirmatrelvir-ritonavir as compared with placebo.*

Subsequent real-world data[13] have shown higher rates (discontinuation at 17.5%) in very small (n=50) cohorts. Ongoing collection of adverse event reports will refine the real-world estimates.

There are multiple possible dangerous drug interactions (many drugs interact with nirmatrelvir-ritonavir especially through CYP3A inhibition, see mechanism of action). Use of nirmatrelvir-ritonavir may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.[7]

A Cochrane review from 2022 assessed the safety or nirmatrelvir,[14] concluding that it little or no effect on treatment-emergent adverse events (RR 0.95, 95% CI 0.82 to 1.10; 1 study, 2224 participants; moderate-certainty evidence), and probably increases treatment-related adverse events such as dysgeusia and diarrhoea during the study period compared to standard of care plus placebo (RR 2.06, 95% CI 1.44 to 2.95; 1 study[10], 2224 participants; moderate-certainty evidence). Compared to placebo, nirmatrelvir-ritonavir decreased discontinuation of study drug due to adverse events (RR 0.49, 95% CI 0.30 to 0.80; 1 study[10], 2224 participants; moderate-certainty evidence). No study results were identified for improvement of clinical status, quality of life, and viral clearance.

Adverse events listed within the SmPC are:

- Common common (≥1/100 to <1/10): dysgeusia, diarrhoea, vomiting

10.1 Contraindications

Nirmatrelvir is contraindicated in patients with a history of clinically significant hypersensitivity to the active substances (nirmatrelvir-ritonavir) or to any of the excipients, and in those with severe hepatic impairment or severe renal impairment.[4]

10.2 Use in specific populations

The WHO strong recommendation in favour does not apply to pregnant people or children. Nirmatrelvir-ritonavir is not licensed by the US FDA for patients younger than 12 years of age or weighing less than 40kg.

11 Summary of available data on comparative cost and cost-effectiveness of the medicine

There is currently no formal cost-effectiveness analysis as part of the WHO guideline. Please see below for changes in market availability which are likely to increase affordability.

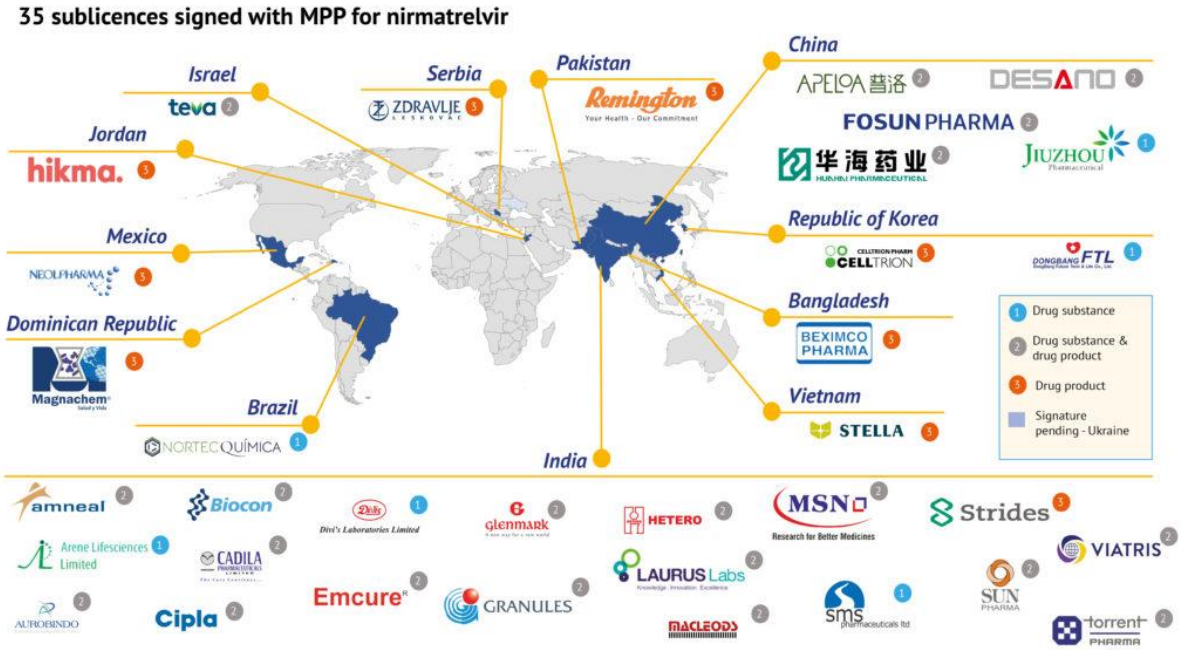
12 Summary of regulatory status and market availability

Currently, this medicine is provided commercially by the patent holder, Pfizer. According to US Institute for Clinical and Economic Review (ICER), the cost for proprietary nirmatrelvir-ritonavir (Paxlovid) in the US is $529.[15] The ACT-Accelerator Transition Plan,[16] is in place to push generic product availability. This is expected from early 2023. Non-peer reviewed estimates from Harvard university estimate costs for generic nirmatrelvir-ritonavir to be US$73.15 per treatment course.[17]

12.1 Medicines Patent Pool (MPP)

The Medicines Patent Pool (MPP) holds a license agreement to provide nirmatrelvir-ritonavir in 95 countries, through 35 companies (see Figure 2).[18] Under this agreement, Pfizer will not receive royalties from sales of nirmatrelvir from the MPP sublicensees while COVID-19 remains classified as a Public Health Emergency of International Concern by the World Health Organization. Following the pandemic period, sales to low-income countries will remain royalty free, lower-middle-income countries and upper-middle-income countries will be subject to a 5% royalty for sales to the public sector and a 10% royalty for sales to the private sector.

Figure 2 – Medicines Patent Pool (MPP) agreements for nirmatrelvir reported on 17 March 2022[19]



12.2 Country list of MPP for nirmatrelvir-ritonavir

The 95 countries covered by the MPP agreements comprise approximately 53% of the world's population. They are:

Afghanistan, Algeria, Angola, Armenia, Bangladesh, Belize, Benin, Bhutan, Bolivia (Plurinational State of), Botswana, Burkina Faso, Burundi, Cabo Verde, Cambodia, Cameroon, Central African Republic, Chad, Comoros, Congo, democratic Republic of the, Congo, Côte d'Ivoire, Djibouti, Egypt, El Salvador, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia (the), Georgia, Ghana, Guatemala, Guinea, Guinea-Bissau, Haiti, Honduras, India, Indonesia, Iran (Islamic Republic of), Jordan, Kenya, Kiribati,

Korea (Democratic People's Republic of), Kosovo, Kyrgyzstan, Lao People's Democratic Republic (the), Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Micronesia (Federated States of), Moldova, Republic of, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Papua New Guinea, Philippines, Rwanda, Samoa, Sao Tome and Principe, Senegal, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sri Lanka, State of Palestine, Sudan, Syrian Arab Republic, Tajikistan, Tanzania, United Republic of, Timor-Leste, Togo, Tonga, Tunisia, Uganda, Ukraine, Uzbekistan, Vanuatu, Venezuela (Bolivarian Republic of), Viet Nam, Yemen, Zambia, Zimbabwe

13 Availability of pharmacopoeia standards

Nirmatrelvir-ritonavir is listed in the British National Formulary with a specific indication for Covid-19.[20]

14 References

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