Promoting the Quality of Medicines Plus (PQM+)

Scientific and technical information package for COVID-19 antivirals prescribed to prevent serious disease and death in high-risk populations infected with COVID-19

Nirmatrelvir Tablets co-packaged with Ritonavir Tablet; Molnupiravir Capsule

August 2023

Information package guidance

USAID FROM THE AMERICAN PEOPLE

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Contents

Acknowledgements

European Medicines Agency (EMA) authored documents are cited in their original form as published by EMA (either as a PDF or online publication).

U.S. Food and Drug Administration (FDA) authored documents are cited in their original form as published by U.S. FDA. Advisory committee briefing documents provided to the U.S. FDA by Pfizer and Merck Sharp & Dohme LLC are for public release and were published on the U.S. FDA website.

U.S. National Institutes of Health (NIH) documents were authored by the COVID-19 Treatment Guidelines Panel. Specifically, the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health available at https://www.covid19treatmentguidelines.nih.gov/. Accessed June 1, 2023. The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in these guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website (https://www.covid19treatmentguidelines.nih.gov/).

World Health Organization (WHO)-authored documents are cited in their original form as published by WHO (either as a PDF or online publication). Individual titles, place of publication, and year are contained in each original document except the one listed below. All documents were issued under License: CC BY-NC-SA 3.0 IGO

PQM+ would like to thank our implementing partner programs, Meeting Targets and Maintaining Epidemic Control (EpiC) and Reaching Impact, Saturation, and Epidemic Control (RISE), for their collaboration and support throughout the test-to-treat (T2T) program. We would also like to thank our collaborators from the national medicines regulatory authorities (NMRA) in each of the Test to Treat countries:

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Acronyms

API	active pharmaceutical ingredients
EMA	European Medicines Agency
EUA	emergency use authorization
EUAL	emergency use assessment and listing
EUL	emergency use listing
FDA	U.S. Food and Drug Administration
NIH	U.S. National Institutes for Health
PHEIC	public health emergency of international concern
PQM+	Promoting the Quality of Medicines Plus
T2T	test-to-treat
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Introduction

In May 2022, the United States Agency for International Development (USAID) introduced the test-to-treat programming (T2T) in ten priority countries for populations at high risk of severe illness from COVID-19. COVID-19 antivirals, specifically nirmatrelvir (co-packaged with ritonavir) and molnupiravir, are being prescribed to prevent serious disease and death in high-risk populations when administered early in an infection. The T2T program has been designed to detect infections early and provide COVID-19 antivirals at the time of detection. This design allows for outpatient treatment prior to severe disease progression, eliminating or reducing the need for hospitalization and ultimately reducing the burden on health systems.

The Promoting the Quality of Medicines Plus (PQM+) program , which is funded by USAID and led by U.S. Pharmacopeial Convention (USP), is supporting the T2T initiative by facilitating product registration of COVID-19 therapeutics in the ten priority countries identified by USAID. National Medicines Regulatory Authorities (NMRAs) in low- and middle-income countries (LMICs) are facing many challenges with respect to approvals of COVID-19 therapeutics, including the following:

1. Concerns with the available data to support the safety and efficacy profiles of COVID-19 therapeutics.
2. As a result of emergency health declarations for the COVID-19 pandemic, emergency use authorizations (EUAs) were issued by NMRAs for temporary and emergency availability of COVID-19 therapeutics. However, the World Health Organization (WHO) declared in May 2023 that the COVID-19 pandemic is no longer a public health emergency of international concern and is instead an established and ongoing health issue that requires long-term management. As emergency health declarations end for individual countries, NMRAs will need to re-evaluate authorizations of COVID-19 therapeutics to either revoke EUAs or provide full marketing authorization/approval, since COVID-19 antiviral availability will remain a critical treatment option for COVID-19 even after the end of emergency health declarations.

To help address these two challenges, PQM+ has prepared this information package to assist NMRAs (including, but not limited to, the ten T2T priority countries) in making informed regulatory decisions on market authorization/approval of nirmatrelvir (co-packaged with ritonavir) and molnupiravir. The information package is also useful for manufacturers/applicants, procurement agencies (national, regional, and international), donor communities, and healthcare providers as it's a compilation of relevant data and scientific recommendations concerning the safety, efficacy, and use of the two antiviral products. **Table 1** (on following page) lists the specific drug products that have been approved or authorized by a stringent regulatory authority (including under an EUA) and/or have received prequalification status from WHO.

[1] https://www.usaid.gov/news-information/press-releases/may-12-2022-second-global-covid-19-summit-usaid-announces-220-million-commitment
[2] Bangladesh, Botswana, Cote D'Ivoire, El Salvador, Ghana, Lesotho, Malawi, Mozambique, Rwanda, and Senegal.
[3] https://www.usp-pqmplus.org/
[4] https://www.who.int/europe/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

Table 1. Available COVID-19 Antivirals[5]

ANTIVIRAL	MANUFACTURER	PRODUCT
Nirmatrelvir (150 mg, 2 tablets), co-packaged with ritonavir (100 mg tablet)	Pfizer, USA	**Paxlovid**
	Hetero Labs Ltd., India	**Nirmacom**
Molnupiravir (200 mg capsule)	Merck Sharp & Dohme LLC, USA	**Lagevrio**
	Hetero Labs Ltd., India	**Movfor**
	Emcure Pharmaceuticals Ltd., India	**Lizuvira**
	Dr. Reddy's Laboratories Ltd., India	**Molflu**

Information Package Contents

The contents of this information package have been organized by general information on COVID-19 and treatments followed by specific information related to nirmatrelvir (co-packaged with ritonavir) and molnupiravir. The contents include publicly available scientific and regulatory publications obtained directly from government institutions or other reputable sources. In the product-specific sections below, documents are presented in three tiers based on the information they provide.

Tier A is focused on guidance and primary reviews from WHO and regulators including the U.S. National Institutes of Health (NIH), European Medicines Agency (EMA), and U.S. Food and Drug Administration (U.S. FDA).

Tier B is focused on supportive information expanding on the details provided in Tier A including research articles, supplementary regulatory reviews, and regulatory briefing documents. Specific documents related to WHO pre-qualifications will be included in this tier.

Tier C is focused on supplementary documents that provide additional clarity on regulatory decisions or helpful guidance including press releases, authorization letters, decision announcements, guidance for prescribers, frequently asked questions from regulators, and additional supplementary regulatory reviews.

Note that the information package includes the most recent versions of all available documents as of the date of publication (August 2023). URL links for each document are provided in the individual packages and can be used to check for updates so long as the links are maintained by the parent website.

[5] As of the publication date, August 2023

Package 1. General Information

On March 11, 2020, WHO declared the COVID-19 outbreak a pandemic (**document 1.1**) following significant spread of the COVID-19 virus and emergency declarations in countries around the world. Following experience gained in previous outbreaks including Ebola and Zika, WHO updated the Emergency Use Listing (EUL) procedure (**document 1.2**) in August 2022, effectively replacing the Emergency Use Assessment and Listing (EUAL) procedure. The EUL procedure outlines the process by which WHO will assess an unlicensed product to provide temporary approval in the event of an emergency while additional data is being generated. The EUL procedure is to be used during a public health emergency of international concern (PHEIC) or if deemed necessary to protect the public during a public health emergency that does not meet the threshold of a PHIEC.

After 3 years, on May 5, 2023, WHO announced COVID-19 as an established and ongoing health issue which no longer constitutes a PHEIC, effectively ending the pandemic characterization (**document 1.3**). However, concerns around COVID-19 remain as the virus has become an ongoing health concern with potential for periodic regional outbreaks and threats from new variants.

Since the pandemic began, health officials and experts have gained significant knowledge in the prevention, diagnosis, and treatment of COVID-19, with agencies publishing and regularly updating guidance based on the available scientific evidence. One major area of focus is on therapies that reduce the risk of progression to severe disease and hospitalization or death. **Document 1.4** contains recommendations from NIH on general therapeutic management of non-hospitalized adults with COVID-19. **Document 1.5** includes a review and analysis of available data on COVID-19 treatments, including antivirals.

The Liverpool Drug Interactions Group developed an interactive database of drug-drug interactions for Covid-19 therapeutics and vaccines[6]. **Document 1.6** includes the published list of drug-drug interactions with key COVID-19 therapies, including nirmatrelvir/ritonavir and molnupiravir.

Documents 1.7-1.9 provide in vitro data supporting the efficacy of antiviral agents against specific COVID-19 subvariants. **Documents 1.10-1.12** include published articles providing real world observational studies evaluating the safety and efficacy of nirmatrelvir/ritonavir and molnupiravir. Please note observational studies have inherent limitations and may be affected by residual confounding.

The remaining sections will describe documents specific to nirmatrelvir (150 mg, 2 tablets)/ritonavir (100 mg tablet) and molnupiravir (200 mg capsule), two antivirals that are specifically used to prevent severe disease and hospitalization.

[6] https://www.covid19-druginteractions.org/checker

Package 1. Document information (click here to link to package)

#	DOCUMENT TITLE	SOURCE
1.1	WHO declaration of the COVID-19 pandemic	WHO
1.2	WHO Emergency Use Listing Procedure (version 9, August 2022)	WHO
1.3	WHO Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 Pandemic (May 5, 2023)	WHO
1.4	Therapeutic Management of Non-hospitalized Adults with COVID-19 (July 21, 2023 update)	NIH
1.5	Drug Treatments for COVID-19: Living Systematic Review and Network Meta-Analysis	The BMJ
1.6	Liverpool Drug Interactions Group Drug-Drug Interactions with Key COVID-19 Therapies (May 31, 2023 update)	Liverpool Drug Interactions Group
1.7	Efficacy of Antiviral Agents Against the SARS-CoV-2 Omicron Subvariant BA.2	The New England Journal of Medicine
1.8	Remdesivir, Molnupiravir and Nirmatrelvir Remain Active Against SARS-CoV-2 Omicron and Other Variants of Concern	Antiviral Research
1.9	Efficacy of Antiviral Agents Against Omicron Subvariants BQ.1.1 and XBB	The New England Journal of Medicine
1.10	Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalization in Community Coronavirus Disease 2019 Patients (COVID-19)	Clinical Infectious Diseases
1.11	Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2	The Lancet
1.12	Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use	Viruses

Package 2. Nirmatrelvir co-packaged with ritonavir

Pfizer developed the antiviral combination nirmatrelvir (150 mg, 2 tablets) co-packaged with ritonavir (100 mg tablet) for the treatment of COVID-19 under the brand name Paxlovid. The safety and efficacy of the treatment was established primarily through a phase 2/3 clinical trial entitled EPIC-HR with support from non-clinical studies, additional phase 1 and 2/3 clinical trials, and post-market surveillance.

Both U.S. FDA and EMA issued an EUA or conditions of use for Paxlovid in December 2021. EMA issued a conditional marketing authorization January 28, 2022 with full marketing authorization issued February 24, 2023.U.S. FDA issued full approval of Paxlovid on May 25, 2023 for treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

WHO pre-qualified Paxlovid for treatment of COVID-19 in April 2022, and one additional generic product in December 2022 (Nirmacom, manufactured by Hetero Labs Ltd.).

Tier A Documents

Documents 2A.1 and **2A.2** provide guidance from WHO and NIH concerning the use of nirmatrelvir (150 mg, 2 tablets) co-packaged with ritonavir (100 mg tablet) for the treatment of COVID-19 including discussion on the results of EPIC-HR and the overall evidence supporting the safety and efficacy of Paxlovid. NIH also provided expanded guidance specifically for drug-drug interactions between Paxlovid and concomitant medications (**document 2A.3**). In addition to the resources discussed in Package 1, the Liverpool Drugs Interaction Group has also developed a nirmatrelvir/ritonavir specific drug-drug interactions lists for select outpatient medicines and WHO essential medicines (**documents 2A.4 and 2A.5**).

Documents 2A.6 and **2A.7** are the EMA marketing authorization assessment report for Paxlovid and associate product information. **Documents 2A.8** and **2A.9** are the Article 5(3) assessment report and associated conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring addressed to member states issued by EMA.

Document 2A.10-2A.13 are the published U.S. FDA reviews for Paxlovid including the product quality review, integrated review, risk assessment and risk mitigation review(s), and other reviews (excluding proprietary name reviews). **Document 2A.14** is the current approved prescribing information issued by U.S. FDA. **Document 2A.15** is the U.S. FDA original EUA review of Paxlovid and **documents 2A.16** and **2A.17** are the current EUA fact sheets issued by U.S. FDA.

Package 2A. Tier A Document information (click here to link to package)

#	DOCUMENT TITLE	SOURCE
2A.1	Therapeutics and COVID-19: Living Guideline (January 13, 2023) – 6.2 Nirmatrelvir, pages 13-27	WHO
2A.2	NIH Guidance for Ritonavir-Boosted Nirmatrelvir (Paxlovid)	NIH
2A.3	NIH Guidance for Drug-Drug Interactions Between Ritonavir Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications	NIH
2A.4	Liverpool Drug Interactions Group Drug-Drug Interactions with Outpatient Medicines & Nirmatrelvir/ ritonavir (NMV/r)	Liverpool Drug Interactions Group
2A.5	Liverpool Drug Interactions Group Drug-Drug Interactions with Essential Medicines & Nirmatrelvir/ ritonavir (NMV/r)	Liverpool Drug Interactions Group
2A.6	EMA European Public Assessment Report of Paxlovid (updated February 24, 2022)	EMA
2A.7	EMA European Public Assessment Report – Product Information (Annex I-III; updated June 27 2023)	EMA
2A.8	EMA Article 5(3) Assessment Report of Paxlovid (December 16, 2021)	EMA
2A.9	EMA Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for Unauthorized Product Paxlovid (PF-07321332 150 mg and ritonavir 100 mg) Available for Use	EMA
2A.10	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Product Quality Review	U.S. FDA
2A.11	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Integrated Review	U.S. FDA
2A.12	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Risk Assessment and Risk Mitigation Review(s)	U.S. FDA

Package 2A. continued (click here to link to package)

2A.13	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Other Reviews	U.S. FDA
2A.14	U.S. FDA Paxlovid Approval Label	U.S. FDA
2A.15	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets) Center for Drug Evaluation and Research (CDER) Review (December 22, 2021)	U.S. FDA
2A.16	U.S. FDA Fact Sheet for Patients, Parents, and Caregivers Emergency Use Authorization (EUA) of Paxlovid for Coronavirus Disease 2019 (COVID-19)	U.S. FDA
2A.17	U.S. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid	U.S. FDA

Tier B Documents

Document 2B.1 includes the published results of the EPIC-HR clinical trial. The full results of the EPIC-SR clinical trial have not yet been published, however **document 2B.2** includes the Pfizer press release with conclusions and limited additional data from the trial. **Documents 2B.3-2B.6** include published articles related to the rebound effect of Paxlovid. **Documents 2B.7-2B.12** include published articles providing additional real world observational studies evaluating the safety and efficacy of Paxlovid including specific results for vaccinated adults. Please note observational studies have inherent limitations and may be affected by residual confounding.

Document 2B.13 is the U.S. FDA virology review associated with the EUA approval evaluating the non-clinical data supporting the efficacy of Paxlovid against COVID-19 variants.

The U.S. FDA held an Antimicrobial Drugs Advisory Committee Meeting on March 16, 2023, to evaluate the evidence supporting approval of Paxlovid for treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. **Documents 2B.14-2B.17** are resources associated with the Committee Meeting, specifically the briefing documents and meeting minutes.

Documents 2B.18-2B.21 are the WHO published documents associated with pre-qualification of Paxlovid, specifically the WHO Public Assessment Report Parts 1, 2, 5, and 7. WHO also published the Finished Pharmaceutical Product Inspection Report (**Document 2B.22**) for one manufacturing site of Paxlovid, namely Hetero Labs Ltd. – Unit III. The same

report is published in support of pre-qualification of the Hetero Labs Ltd. product, brand named Nirmacom.

Documents 2B.22-2B.31 are the WHO published documents associated with pre-qualification of Nirmacom, including the Finished Pharmaceutical Product Inspection Report, the Active Pharmaceutical Ingredients Inspection Report, and the WHO Public Assessment Report Parts 1-8.

Package 2B. Tier B Document information (click here to link to package)

#	DOCUMENT TITLE	SOURCE
2B.1	Oral Nirmatrelvir for High-Risk, Non-hospitalized Adults with COVID-19	The New England Journal of Medicine
2B.2	Pfizer Press Release: Pfizer Reports Additional Data on PAXLOVID™ Supporting Upcoming New Drug Application Submission to U.S. FDA	Pfizer
2B.3	Characterization of Virologic Rebound Following Nirmatrelvir-Ritonavir Treatment for Coronavirus Disease 2019 (COVID-19)	Clinical Infectious Diseases
2B.4	Nirmatrelvir–Ritonavir and Viral Load Rebound in Covid-19	The New England Journal of Medicine
2B.5	Symptom and Viral Rebound in Untreated SARS-CoV-2 Infection	Annals of Internal Medicine
2B.6	Rebound Phenomenon After Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease 2019 (COVID-19) in High-Risk Persons	Clinical Infectious Diseases
2B.7	Nirmatrelvir Plus Ritonavir for Early COVID-19 in a Large U.S. Health System	Annals of Internal Medicine
2B.8	Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge	The New England Journal of Medicine
2B.9	Effectiveness of Paxlovid in Reducing Severe Coronavirus Disease 2019 and Mortality in High-Risk Patients	Clinical Infectious Diseases
2B.10	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	The Lancet

Package 2B. continued (click here to link to package)

2B.11	Population-based evaluation of the effectiveness of nirmatrelvir–ritonavir for reducing hospital admissions and mortality from COVID-19	Canadian Medial Association Journal
2B.12	Oral Nirmatrelvir and Ritonavir in Nonhospitalized Vaccinated Patients with Coronavirus Disease 2019	Clinical Infectious Diseases
2B.13	U.S. FDA Division of Antivirals, CDER/OND/OID Clinical Virology Review (September 26, 2022)	U.S. FDA
2B.14	U.S. FDA Briefing Document – Antimicrobial Drugs Advisory Committee Meeting (March 16, 2023)	U.S. FDA
2B.15	U.S. FDA Briefing Document Errata – Antimicrobial Drugs Advisory Committee Meeting (March 16, 2023)	U.S. FDA
2B.16	Pfizer Briefing Document – Antimicrobial Drugs Advisory Committee Meeting (March 16, 2023)	Pfizer
2B.17	U.S. FDA Summary Minutes – Antimicrobial Drugs Advisory Committee Meeting (March 16, 2023)	U.S. FDA
2B.18	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – Paxlovid (Part 1)	WHO
2B.19	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – Paxlovid (Part 2)	WHO
2B.20	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – Paxlovid (Part 5)	WHO
2B.21	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – Paxlovid (Part 7)	WHO
2B.22	WHO Prequalification Unit Inspection services WHO Public Inspection Report Desk Assessment of Finished Product Manufacturer – Hetero Labs Ltd. Unit III	WHO
2B.23	WHO Prequalification Unit Inspection services WHO Public Inspection Report Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer – Honour Lab Limited Unit III	WHO
2B.24	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 1)	WHO

Package 2B. continued (click here to link to package)

2B.25	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 2)	WHOI
2B.26	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 3)	WHO
2B.27	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 4)	WHO
2B.28	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 5)	WHO
2B.29	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 6)	WHO
2B.30	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 7)	WHO
2B.31	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV012/Nirmacom (Part 8)	WHO

Tier C Documents

Documents 2C.1-2C.3 include additional supportive documents published by EMA including the medicine overview, procedural steps taken and scientific information after authorization, and advice on the emergency use of Paxlovid adding context to the conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring addressed to member states (**document 2A.5**).

Documents 2C.4-2C.9 include additional supportive documents published by U.S. FDA including the approval letter for Paxlovid (May 25, 2023), the May 25, 2023 press release describing the approval conditions of Paxlovid, administrative and correspondence documents associated with the approval of Paxlovid, current EUA authorization letter for Paxlovid (May 25, 2023), guidance with frequently asked questions on the EUA for Paxlovid for treatment of COVID-19, and a Paxlovid eligibility screening checklist tool for prescribers.

Pfizer also published prescribing and dispensing instructions for healthcare providers

(**document 2C.10**) with the intention of minimizing errors associated with an additional package configuration specifically for patients with moderate renal impairment.

Documents 2C.11-2C.21 include additional U.S. FDA review memorandums providing rationale for changes or updates to the letter of authorization, published fact sheets, and other supportive documents for the EUA of Paxlovid following availability of additional information. All changes discussed in these reviews are reflected in the current EUA fact sheets and approved label for Paxlovid.

Package 2C. Tier C Document information (click here to link to package)

#	DOCUMENT TITLE	SOURCE
2C.1	EMA European Public Assessment Report – Medicine Overview (March 7, 2023)	EMA
2C.2	EMA European Public Assessment Report – Procedural Steps Taken and Scientific Information After Authorisation (June 27, 2023)	EMA
2C.3	EMA News: EMA issues advice on use of Paxlovid (PF-07321332 and ritonavir) for the treatment of COVID-19: rolling review starts in parallel	EMA
2C.4	U.S. FDA Paxlovid Approval Letter	U.S. FDA
2C.5	U.S. FDA News Release: FDA Approves First Oral Antiviral for Treatment of COVID-19 in Adults (May 25, 2023)	U.S. FDA
2C.6	U.S. FDA Center for Drug Evaluation and Research Application number: 217188Orig1s000 Administrative and Correspondence Documents	U.S. FDA
2C.7	U.S. FDA EUA Authorization letter – Paxlovid (May 25, 2023)	U.S. FDA
2C.8	U.S. FDA Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19	U.S. FDA
2C.9	U.S. FDA Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers	Pfizer
2C.10	Pfizer Important Prescribing and Dispensing Information (April 5, 2022)	U.S. FDA

Package 2C. continued (click here to link to package)

2C.11	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (February 23, 2022)	U.S. FDA
2C.12	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (March 18, 2022)	U.S. FDA
2C.13	U.S. FDA Clinical Pharmacology EUA Summary Review (April 8, 2022)	U.S. FDA
2C.14	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (June 28, 2022)	U.S. FDA
2C.15	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (July 6, 2022)	U.S. FDA
2C.16	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (August 5, 2022)	U.S. FDA
2C.17	U.S. FDA Clinical Pharmacology EUA Summary Review (August 25, 2022)	U.S. FDA
2C.18	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (September 26, 2022)	U.S. FDA
2C.19	U.S. FDA Memorandum: Summary Basis for Revising Certain Conditions on Printed, Advertising and Promotional Materials (October 27, 2022)	U.S. FDA
2C.20	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (February 1, 2023)	U.S. FDA
2C.21	U.S. FDA Emergency Use Authorization (EUA) for Paxlovid Center for Drug Evaluation and Research (CDER) Review Memorandum (May 25, 2023)	U.S. FDA

Package 3. Molnupiravir

Merck Sharp & Dohme LLC developed the antiviral molnupiravir (200 mg capsule) for the treatment of COVID-19 under the brand name Lagevrio. The safety and efficacy of the treatment was established primarily through a phase 3 clinical trial entitled MOVe-OUT with additional support from an open-label phase 3 clinical trial entitled PANORAMIC, non-clinical studies, additional phase 1 and 2 clinical trials, and post-market surveillance.

Both EMA and U.S. FDA issued an EUA or conditions of use for Lagevrio in November and December 2021 respectively. On February 23, 2023, EMA issued a refusal of the marketing application for Lagevrio citing that, based on available data, EMA could not conclude that Lagevrio reduced the risk of hospitalization or death or shortened the duration of illness or time to recovery in adults at risk of severe disease. In addition, they could not identify a specific sub-population of patients with demonstratable benefits from Lagevrio. On March 13, 2023, Merck Sharp & Dohme B.V. requested a re-examination of EMA's opinion; on June 21, 2023 Merck Sharp & Dohme B.V. withdrew the application for marketing authorization of Lagevrio.

WHO pre-qualified three additional generic products in September 2022 (Movfor manufactured by Hetero Labs Ltd.), December 2022 (Lizuvria manufactured by Emcure Pharmaceuticals Ltd.), and April 2023 (Molflu manufactured by Dr. Reddy's Laboratories Ltd.).

Tier A Documents

Documents 3A.1 and 3A.2 provide guidance from WHO and NIH concerning the use of molnupiravir (200 mg capsules) for the treatment of COVID-19 including discussion on the results of MOVe-OUT and the overall evidence supporting the safety and efficacy of Lagevrio.

Documents 3A.3 is the EMA withdrawal assessment report, **document 3A.4** is the EMA Article 5(3) assessment report for Lagevrio, and **document 3A.5** is the associated conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring addressed to member states issued by EMA.

Document 3A.6 is the U.S. FDA original EUA review of Paxlovid, **document 3A.7** is a continuing review memo issued February 2023, and **documents 3A.8** and **3A.9** are the current EUA fact sheets issued by U.S. FDA.

Package 3A. Tier A Document information (click to link to package)

#	DOCUMENT TITLE	SOURCE
3A.1	Therapeutics and COVID-19: Living Guideline (January 13, 2023) – 6.9 Molnupiravir, pages 70-77	WHO
3A.2	NIH Guidance for Molnupiravir	NIH

Package 3A. continued (click here to link to package)

3A.3	EMA Withdrawal Assessment Report, Lagevrio (February 23, 2023)	EMA
3A.4	EMA Assessment Report of Lagevrio (January 27, 2022)	EMA
3A.5	EMA Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for Unauthorized Product Lagevrio (molnupiravir) Available for Use	EMA
3A.6	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review (December 23, 2021)	U.S. FDA
3A.7	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (February 17, 2023)	U.S. FDA
3A.8	U.S. FDA Fact Sheet for Patients and Caregivers Emergency Use Authorization (EUA) of Lagevrio (molnupiravir) capsules for Coronavirus Disease 2019 (COVID-19)	U.S. FDA
3A.9	U.S. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio (molnupiravir) Capsules	U.S. FDA

Tier B Documents

Document 3B.1 includes the published results of the MOVe-OUT clinical trial and **document 3B.2** includes the published results of the PANORAMIC clinical trial. Documents 3B.3-3B.5 include published articles providing additional real world observational studies evaluating the safety and efficacy of Lagevrio including specific results for vaccinated adults. Please note observational studies have inherent limitations and may be affected by residual confounding.

Document 3B.6 is the U.S. FDA virology review associated with the EUA approval evaluating the clinical and non-clinical data for potential COVID-19 rebound or re-infection following administration of molnupiravir. **Document 3B.7** is a continuing review from the U.S. FDA evaluating information regarding the post-authorization report of cases of hypersensitivity reactions and rash events in association with molnupiravir use.

The U.S. FDA held an Antimicrobial Drugs Advisory Committee Meeting on November 20, 2021 to evaluate the evidence supporting emergency use of Lagevrio for treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 and/or hospitalization. **Documents 3B.8-3B.13** are resources associated with the Committee Meeting, specifically briefing documents and meeting minutes.

Documents 3B.14-3B.23 are the WHO published documents associated with pre-qualification of Movfor, including the Finished Pharmaceutical Product Inspection Report, the Active Pharmaceutical Ingredients Inspection Report, and the WHO Public Assessment Report Parts 1-8.

Documents 3B.24-3B.33 are the WHO published documents associated with pre-qualification of Molflu, including the Finished Pharmaceutical Product Inspection Report, the Active Pharmaceutical Ingredients Inspection Report, and the WHO Public Assessment Report Parts 1-8.

The WHO Active Pharmaceutical Ingredients Inspection Report associated with pre-qualification of Lizuvira is the same report associated with pre-qualification of Movfor (**Document 3B.15**). **Documents 3B.34-3B.40** are the WHO Public Assessment Report Parts 1-8.

Package 3B. Tier B Document information (click here to link to package)

#	DOCUMENT TITLE	SOURCE
3B.1	Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalized Patients	The New England Journal of Medicine
3B.2	Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform adaptive randomised controlled trial	The Lancet
3B.3	Effectiveness of Molnupiravir in High-Risk Patients: A Propensity Score Matched Analysis	Clinical Infectious Diseases
3B.4	Real-world experience with molnupiravir during the period of SARS-CoV-2 Omicron variant dominance	Pharmacological Reports
3B.5	Molnupiravir Use and 30-Day Hospitalizations or Death in a Previously Uninfected Nonhospitalized High-risk Population With COVID-19	The Journal of Infectious Diseases

Package 3B. continued (click here to link to package)

3B.6	U.S. FDA Division of Antivirals, CDER/OND/OID Clinical Virology Review (August 2, 2022)	U.S. FDA
3B.7	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum(February 11, 2022)	U.S. FDA
3B.8	U.S. FDA Briefing Document – Antimicrobial Drugs Advisory Committee Meeting (November 30, 2021)	U.S. FDA
3B.9	U.S. FDA Briefing Document Errata – Antimicrobial Drugs Advisory Committee Meeting (November 30, 2021)	U.S. FDA
3B.10	U.S. FDA Briefing Document Addendum – Antimicrobial Drugs Advisory Committee Meeting (November 30, 2021)	U.S. FDA
3B.11	Merck Briefing Document – Antimicrobial Drugs Advisory Committee Meeting (November 30, 2021)	Merck
3B.12	Merck Briefing Document Addendum– Antimicrobial Drugs Advisory Committee Meeting (November 30, 2021)	U.S. FDA
3B.13	U.S. FDA Summary Minutes – Antimicrobial Drugs Advisory Committee Meeting (November 30, 2021)	WHO
3B.14	WHO Prequalification Unit Inspection services WHO Public Inspection Report Desk Assessment of Finished Product Manufacturer – Hetero Labs Ltd. Unit 5	WHO
3B.15	WHO Prequalification Unit Inspection services WHO Public Inspection Report Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer – Honour Lab Limited Unit III	WHO
3B.16	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 1)	WHO
3B.17	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 2)	WHO
3B.18	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 3)	WHO

Package 3B. continued (click here to link to package)

3B.19	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 4)	WHO
3B.20	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 5)	WHO
3B.21	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 6)	WHO
3B.22	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 7)	WHO
3B.23	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV008/Movfor (Part 8)	WHO
3B.24	WHO Prequalification Unit Inspection services WHO Public Inspection Report Desk Assessment of Finished Product Manufacturer – Formulations Technical Operations Unit 2, Dr. Reddy's Laboratories Ltd	WHO
3B.25	WHO Prequalification Unit Inspection services WHO Public Inspection Report Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer – Divi's Laboratories Limited, Unit 1	WHO
3B.26	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 1)	WHO
3B.27	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 2)	WHO
3B.28	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 3)	WHO
3B.29	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 4)	WHO
3B.30	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 5)	WHO
3B.31	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 6)	WHO

Package 3B. continued (click here to link to package)

3B.32	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 7)	WHO
3B.33	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV009/Molflu (Part 8)	WHO
3B.34	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 1)	WHO
3B.35	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 2)	WHO
3B.36	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 3)	WHO
3B.37	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 4)	WHO
3B.38	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 5)	WHO
3B.39	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 6)	WHO
3B.40	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 7)	WHO
3B.41	WHO Prequalification Programme WHO Public Assessment Report (WHOPAR) – CV010/Lizuvira (Part 8)	WHO

Tier C Documents

Document 3C.1 includes the EMA announcement for the refusal of the marketing application for Lagevrio, however, EMA has not published a full review describing their decision making or the data relied upon. **Documents 3C.2** and **3C.3** include the EMA questions and answers on the withdrawal of the application for marketing authorization of Lagevrio and the withdrawal letter from Merck Sharp and Dohme B.V. The conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring addressed to member states issued by EMA (**document 3A.4**) is still published on the EMA website and noted as adopted.

Documents 3C.4-3C.6 include additional supportive documents published by the U.S. FDA including the current EUA authorization letter for Lagevrio (February 1, 2023), guidance with frequently asked questions on the emergency use authorization for Lagevrio (molnupiravir) for treatment of COVID-19, and a Molnupiravir checklist tool for prescribers.

Documents 3C.7-3C.8 include additional U.S. FDA review memorandums providing rational for changes or updates to the published fact sheets or other supportive documents for the EUA of Lagevrio following availability of additional information. All changes discussed in these reviews are reflected in the current EUA fact sheets and documents.

Package 3C. Tier C Document information (click here to link to package)

#	DOCUMENT TITLE	SOURCE
3C.1	EMA Refusal of the marketing authorisation for Lagevrio (molnupiravir)	EMA
3C.2	EMA Question and Answers on Withdrawal of Application for the Marketing Authorization of Lagevrio (molnupiravir)	EMA
3C.3	Letter for the Withdrawal of Marketing Authorization Application for Lagevrio, molnupiravir, 200 mg hard capsules, EMEA/H/C/005789	Merck
3C.4	U.S. FDA EUA Authorization letter – Lagevrio (February 1, 2023)	U.S. FDA
3C.5	U.S. FDA Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19	U.S. FDA
3C.6	U.S. FDA Molnupiravir checklist tool for prescribers	U.S. FDA
3C.7	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (March 23, 2022)	U.S. FDA
3C.8	U.S. FDA Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules Center for Drug Evaluation and Research (CDER) Review Memorandum (February 1, 2023)	U.S. FDA

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