Pfizer Logo

Pfizer Receives CHMP Positive Opinion for Novel COVID-19 Oral Treatment

Thursday, January 27, 2022 - 09:11am

- *CHMP recommends PAXLOVID™ (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) for use in adults with COVID-19*
- *If authorized, PAXLOVID will be the first COVID-19 oral treatment recommended in the EU*
- *European Commission decision on conditional marketing authorization expected imminently*

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending the conditional marketing authorization (CMA) of Pfizer's PAXLOVID™ (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

"This expression of confidence in PAXLOVID comes at a critical moment as Europe addresses the ongoing challenges of the pandemic and as infection rates are on the rise in many countries across the globe," said Albert Bourla, Chairman and Chief Executive Officer, Pfizer. "We are proud to have a strong manufacturing footprint in Europe, which will help support the production of up to 120 million courses of PAXLOVID globally. Pending conditional marketing authorization from the European Commission, we will continue working closely with EU Member State governments to ensure this important treatment can be made available to patients across Europe as quickly as possible."

The CHMP based its positive opinion on the scientific evidence supporting PAXLOVID, including data from the Phase 2/3 EPIC-HR (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients) trial, which enrolled non-hospitalized adults aged 18 and older with confirmed COVID-19 who are at increased risk of progressing to severe illness. The data showed that PAXLOVID reduced the risk of hospitalization or death by 89% (within three days of symptom onset) and 88% (within five days of symptom onset) compared to placebo, with no deaths observed in the treatment group. Treatment-emergent adverse events were comparable between PAXLOVID (23%) and placebo (24%), most of which were mild in intensity. The data have been submitted to a peer-reviewed publication. Additional Phase 2/3 clinical trials are ongoing in adults at standard risk (i.e., low risk of hospitalization or death) of progressing to severe illness, and in those who have been exposed to the virus through household contacts.

PAXLOVID is currently approved or authorized for emergency use in more than 10 countries across the globe. In December, the CHMP issued advice under Article 5(3) of Regulation 726/2004 to support authorities of European Union (EU) Member States regarding the potential supply and use of PAXLOVID prior to EU conditional marketing authorization.

Our Commitment to Equitable Access

Pfizer is committed to working toward equitable access to PAXLOVID for all people, aiming to deliver safe and effective antiviral therapeutics as soon as possible and at an affordable price. During the pandemic, Pfizer will offer its oral therapy through a tiered pricing approach, pending country authorization or approval, based on the income level of each country to promote equity of access across the globe. High and upper-middle income countries will pay more than lower income countries.

Pfizer continues to invest to support the manufacturing and distribution of PAXLOVID, including exploring potential contract manufacturing options. As a result of these efforts, Pfizer has raised its production projections, with the potential ability to produce up to 120 million courses of treatment by the end of 2022.

The company has entered into agreements with multiple countries and has initiated bilateral outreach to more than 100 countries around the world. Additionally, Pfizer has signed a voluntary license agreement with the Medicines Patent Pool (MPP) for its oral treatment to help expand access, pending country regulatory authorization or approval, in 95 low- and middle-income countries that account for approximately 53% of the world's population.

About PAXLOVID™ (nirmatrelvir [PF-07321332] tablets and ritonavir tablets)

PAXLOVID is a SARS-CoV-2 main protease (M^{pro}) inhibitor (also known as SARS-CoV2 3CL protease inhibitor) therapy. It was developed to be administered orally so that it can be prescribed at the first sign of infection or, pending clinical success of the rest of the EPIC development program and subject to regulatory authorization, at first awareness of an exposure – potentially helping patients avoid severe illness (which can lead to hospitalization and death) or avoid disease development following contact with a household member who contracts COVID-19. Nirmatrelvir [PF-07321332], which originated in Pfizer laboratories, is designed to block the activity of the M^{pro}, an enzyme that the coronavirus needs to replicate. Co-administration with a low dose of ritonavir helps slow the metabolism, or breakdown, of nirmatrelvir in order for it to remain active in the body for longer periods of time at higher concentrations to help combat the virus.

Nirmatrelvir is designed to inhibit viral replication at a stage known as proteolysis, which occurs before viral RNA replication. In preclinical studies, nirmatrelvir did not demonstrate evidence of mutagenic DNA interactions.

Current variants of concern can be resistant to treatments that work by binding to the spike protein found on the surface of the SARS-CoV-2 virus. PAXLOVID, however, works intracellularly by binding to the highly conserved M^{pro} of the SARS-CoV-2 virus to inhibit viral replication. Nirmatrelvir has shown consistent in vitro antiviral activity against earlier and current variants of concern (i.e., Alpha, Beta, Delta, Gamma, Lambda, Mu, and Omicron).

PAXLOVID is administered at a dose of 300 mg (two 150 mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir, given twice-daily for five days. One carton contains five blister packs of PAXLOVID, as co-packaged nirmatrelvir tablets with ritonavir tablets, providing all required doses for a full five-day treatment course.

About the EPIC Development Program

The EPIC (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19) Phase 2/3 development program for PAXLOVID consists of three clinical trials spanning a broad spectrum of patients, including adults who have been exposed to the virus through household contacts, as well as adults at both standard risk and high risk of progressing to severe illness.?

In July 2021, Pfizer initiated the first of these trials, known as EPIC-HR, a randomized, double-blind study of non-hospitalized adults with COVID-19, who are at high risk of progressing to severe illness. At the

recommendation of an independent Data Monitoring Committee and in consultation with the U.S. FDA, Pfizer ceased further enrollment into the study in early November 2021 due to the overwhelming efficacy demonstrated in these results. Findings from the EPIC-HR final analysis have been submitted to a peer-reviewed journal for publication.

In August 2021, Pfizer began the Phase 2/3 EPIC-SR (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **S**tandard-**R**isk Patients), to evaluate efficacy and safety in adults with a confirmed diagnosis of SARS-CoV-2 infection who are at standard risk (i.e., low risk of hospitalization or death). EPIC-SR includes a cohort of vaccinated adults who have an acute breakthrough symptomatic COVID-19 infection and who have risk factors for severe illness. Interim data from this study have been reported. In September, Pfizer initiated the Phase 2/3 EPIC-PEP (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **P**ost-**E**xposure **P**rophylaxis) to evaluate efficacy and safety in adults exposed to SARS-CoV-2 by a household member. These trials are ongoing.

For more information on the EPIC Phase 2/3 clinical trials for PAXLOVID, visit clinicaltrials.gov.

About the EPIC-HR Final Results

In the final analysis of the primary endpoint from all patients enrolled in EPIC-HR, an 89% reduction in COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset was observed, consistent with the interim analysis. In addition, a consistent safety profile was observed.

0.7% of patients who received PAXLOVID were hospitalized through Day 28 following randomization (5/697 hospitalized with no deaths), compared to 6.5% of patients who received placebo and were hospitalized or died (44/682 hospitalized with 9 subsequent deaths). The statistical significance of these results was high ($p<0.0001$). In a secondary endpoint, PAXLOVID reduced the risk of hospitalization or death for any cause by 88% compared to placebo in patients treated within five days of symptom onset; 0.8% of patients who received PAXLOVID were hospitalized or died through Day 28 following randomization (8/1039 hospitalized with no deaths), compared to 6.3% of patients who received placebo (66/1046 hospitalized with 12 subsequent deaths), with high statistical significance ($p<0.0001$). Relative risk reduction was 94% in patients 65 years of age or older, one of the populations at highest risk for hospitalization or death; 1.1% of patients who received PAXLOVID were hospitalized through Day 28 (1/94 hospitalized with no deaths), compared to 16.3% of patients who received placebo (16/98 hospitalized with 6 deaths), with high statistical significance ($p<0.0001$). In the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID as compared to 12 (1.2%) deaths in patients who received placebo.

In the EPIC-HR trial, in a secondary endpoint, SARS-CoV-2 viral load at baseline and Day 5 have been evaluated for 499 patients. After accounting for baseline viral load, geographic region, and serology status, PAXLOVID reduced viral load by approximately 10-fold relative to placebo, indicating robust activity against SARS-CoV-2 and representing the strongest viral load reduction reported to date for an oral COVID-19 agent.

Treatment-emergent adverse events were comparable between PAXLOVID (23%) and placebo (24%), most of which were mild in intensity. Fewer serious adverse events (1.6% vs. 6.6%) and discontinuation of study drug due to adverse events (2.1% vs. 4.2%) were observed in patients dosed with PAXLOVID, compared to placebo, respectively.

All other secondary endpoints for this study, which are available on clinicaltrials.gov (NCT04960202) and EudraCT (2021-002895-38), were not yet available for this review.

U.S. FDA Emergency Use Authorization Statement

PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death.

The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product PAXLOVID for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19
- PAXLOVID is not authorized for use for longer than 5 consecutive days

PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).

PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under 564(b)(1) of the Food Drug and Cosmetic Act unless the authorization is terminated or revoked sooner.

IMPORTANT SAFETY INFORMATION

PAXLOVID is **contraindicated in patients with a history of clinically significant hypersensitivity reactions** (eg, toxic epidermal necrolysis [TEN] or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is **contraindicated with drugs that are highly dependent on CYP3A** for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:

- $Alpha_1$-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine

- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID is **contraindicated with drugs that are potent CYP3A inducers** where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

- Anticancer agents: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal Products: St. John's Wort (*hypericum perforatum*)

There are limited clinical data available for PAXLOVID. **Serious and unexpected adverse events may occur** that have not been previously reported with PAXLOVID use.

Risk of Serious Adverse Reactions Due to Drug Interactions: Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PAXLOVID, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications
- Clinically significant adverse reactions from greater exposures of PAXLOVID
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance

Consult Table 1 of the Fact Sheet for Healthcare Providers for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with **pre-existing liver diseases, liver enzyme abnormalities, or hepatitis**.

Because nirmatrelvir is co-administered with ritonavir, there may be a **risk ofHIV-1 developing resistance to HIV protease inhibitors** in individuals with uncontrolled or undiagnosed HIV-1 infection.

Adverse events in the PAXLOVID group (?1%) that occurred at a greater frequency (?5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), and hypertension (1% and <1%), and myalgia (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

Required Reporting for Serious Adverse Events and Medication Errors: The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events and medication errors potentially related to PAXLOVID within 7 calendar days from the onset of the event.

Submit adverse event and medication error reports to FDA MedWatch using one of the following methods:

- **Online:** https://www.fda.gov/medwatch/report.htm
- **Complete and submit a postage-paid** FDA Form 3500 **and returning by mail/fax**
- **Call** 1-800-FDA-1088 **to request a reporting form**

In addition, please provide a copy of all FDA MedWatch forms to: www.pfizersafetyreporting.com, or by fax (1-866-635-8337) or phone (1-800-438-1985).

PAXLOVID is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CPY3A substrates may require a dose adjustment or additional monitoring.

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

Pregnancy: There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug?associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug?associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy.

Lactation: There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID?19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID?19.

Contraception: Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

Pediatrics: PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR.

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment. No dosage adjustment is needed in patients with mild renal impairment. **In patients with moderate renal impairment (eGFR ?30 to <60 mL/min), reduce the dose of PAXLOVID** to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Providers should counsel patients about renal dosing instructions. **PAXLOVID is not recommended in patients with severe renal impairment** (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been

determined.

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, **PAXLOVID is not recommended for use in patients with severe hepatic impairment.**

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 170 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Disclosure Notice

The information contained in this statement is as of January 27, 2022. Pfizer assumes no obligation to update forward-looking statements contained in this statement as the result of new information or future events or developments.

This statement contains forward-looking information about Pfizer's efforts to combat COVID-19 and PAXLOVID (including a potential CMA in the EU, qualitative assessments of available data, potential benefits, expectations for clinical trials, advanced purchase agreements and an agreement with MPP, efforts toward equitable access, the anticipated timing of data readouts, regulatory submissions, regulatory approvals or authorizations, potential to maintain antiviral activity against variants, planned investment and anticipated manufacturing, distribution and supply), involving substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as risks associated with preclinical and clinical data, including the possibility of unfavorable new preclinical, clinical or safety data and further analyses of existing preclinical, clinical or safety data, including the risk that final results from EPIC-SR could differ from the interim data; the ability to produce comparable clinical or other results including efficacy, safety and tolerability profile observed to date, in additional studies or in larger, more diverse populations following commercialization; the ability of PAXLOVID to maintain efficacy against emerging virus variants; the risk that serious and unexpected adverse events may occur that have not been previously reported with PAXLOVID use; the risk that preclinical and clinical trial data are subject to differing interpretations and assessments, including during the peer review/publication process, in the scientific community generally, and by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from these and any future preclinical and clinical studies; whether and when any drug applications or submissions to request emergency use or conditional marketing authorization for any potential indications for PAXLOVID may be filed in particular jurisdictions and if obtained, whether or when such emergency use authorization or licenses will expire or terminate; whether and when regulatory authorities in any jurisdictions may approve any applications

or submissions for PAXLOVID that may be pending or filed (including the application for conditional marketing authorization pending in the EU, a potential new drug application submission in the U.S. and submissions in other jurisdictions), which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether it will be commercially successful; decisions by regulatory authorities impacting labeling or marketing, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of PAXLOVID, including development of products or therapies by other companies; risks related to the availability of raw materials for PAXLOVID; the risk that we may not be able to create or scale up manufacturing capacity on a timely basis or maintain access to logistics or supply channels commensurate with global demand, which would negatively impact our ability to supply the estimated numbers of courses of PAXLOVID within the projected time periods; whether and when additional purchase agreements will be reached; the risk that demand for any products may be reduced or no longer exist; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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Source: Pfizer Inc.