Pfizer Responds to Research Claims

Friday, January 27, 2023 - 08:00pm

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New York, N.Y., January 27, 2023 – Allegations have recently been made related to gain of function and directed evolution research at Pfizer and the company would like to set the record straight.

In the ongoing development of the Pfizer-BioNTech COVID-19 vaccine, Pfizer has not conducted gain of function or directed evolution research. Working with collaborators, we have conducted research where the original SARS-CoV-2 virus has been used to express the spike protein from new variants of concern. This work is undertaken once a new variant of concern has been identified by public health authorities. This research provides a way for us to rapidly assess the ability of an existing vaccine to induce antibodies that neutralize a newly identified variant of concern. We then make this data available through peer reviewed scientific journals and use it as one of the steps to determine whether a vaccine update is required.

In addition, to meet U.S. and global regulatory requirements for our oral treatment, PAXLOVID™, Pfizer undertakes in vitro work (e.g., in a laboratory culture dish) to identify potential resistance mutations to nirmatrelvir, one of PAXLOVID's two components. With a naturally evolving virus, it is important to routinely assess the activity of an antiviral. Most of this work is conducted using computer simulations or mutations of the main protease–a non-infectious part of the virus. In a limited number of cases when a full virus does not contain any known gain of function mutations, such virus may be engineered to enable the assessment of antiviral activity in cells. In addition, in vitro resistance selection experiments are undertaken in cells incubated with SARS-CoV-2 and nirmatrelvir in our secure Biosafety level 3 (BSL3) laboratory to assess whether the main protease can mutate to yield resistant strains of the virus. It is important to note that these studies are required by U.S. and global regulators for all antiviral products and are carried out by many companies and academic institutions in the U.S. and around the world.

Fact-based information rooted in sound science is vitally important to overcoming the COVID-19 pandemic and Pfizer remains committed to transparency and helping alleviate the devastating burden of this disease.

U.S. INDICATION & AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is FDA authorized under Emergency Use Authorization (EUA) for use in individuals 5 years of age and older as a single booster dose administered at least 2 months after either:

- completion of primary vaccination with any authorized or approved monovalent* COVID-19 vaccine; or
- receipt of the most recent booster dose with any authorized or approved monovalent* COVID-19 vaccine

*Monovalent refers to any authorized and approved COVID-19 vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2 virus.

COMIRNATY® (COVID-19 Vaccine, mRNA)

INDICATION
COMIRNATY® (COVID-19 Vaccine, mRNA) is an FDA-approved COVID-19 vaccine for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

AUTHORIZED USE
COMIRNATY® (COVID-19 Vaccine, mRNA) is authorized under Emergency Use Authorization (EUA) to provide:

Primary Series

- a third primary series dose to individuals 12 years of age and older who have certain kinds of immunocompromise

Pfizer-BioNTech COVID-19 Vaccine

AUTHORIZED USES

Pfizer-BioNTech COVID-19 Vaccine is FDA authorized under Emergency Use Authorization (EUA) for use in individuals 6 months and older to provide:

Primary Series

- a 2-dose primary series to individuals 5 years of age and older
- a third primary series dose to individuals 5 years of age and older with certain kinds of immunocompromise

Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent

AUTHORIZED USES

Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent are FDA authorized under Emergency Use Authorization (EUA) for use in individuals 6 months to 4 years of age to provide:

Primary Series

- a 3-dose primary series as follows:
  - Dose 1: Pfizer-BioNTech COVID-19 Vaccine
  - Dose 2: Pfizer-BioNTech COVID-19 Vaccine
  - Dose 3: Pfizer-BioNTech COVID-19 Vaccine, Bivalent

EMERGENCY USE AUTHORIZATION

Emergency uses of the vaccines have not been approved or licensed by FDA but have been authorized by FDA under an Emergency Use Authorization (EUA) to prevent Coronavirus Disease 2019 (COVID-19) in individuals aged 6 months and older. The emergency uses are only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

IMPORTANT SAFETY INFORMATION

Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), COMIRNATY® (COVID-19 Vaccine, mRNA), and Pfizer-BioNTech COVID-19 Vaccine

Tell your vaccination provider about all of your medical conditions, including if you:

- have any allergies
- have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart)
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects the immune system
- are pregnant, plan to become pregnant, or are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

- The vaccine may not protect everyone

- You should not get COMIRNATY (COVID-19 Vaccine, mRNA), the Pfizer-BioNTech COVID-19 Vaccine, or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent if you have had a severe allergic reaction after a previous dose of COMIRNATY or the Pfizer-BioNTech COVID-19 Vaccine or any ingredient in these vaccines

- There is a remote chance that these vaccines could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to 1 hour after getting a dose of the vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received the vaccine for monitoring after vaccination. If you experience a severe allergic reaction, call 9-1-1 or go to the nearest hospital

Seek medical attention right away if you have any of the following symptoms:

- difficulty breathing, swelling of the face and throat, a fast heartbeat, a bad rash all over the body, dizziness, and weakness

- Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received COMIRNATY® (COVID-19 vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine. The observed risk is higher among adolescent males and adult males under 40 years of age than among females and older males, and the observed risk is highest in males 12 through 17 years of age. In most of these people, symptoms began within a few days following receipt of the second dose of vaccine. The chance of having this occur is very low

- Side effects that have been reported with these vaccines include:

- Severe allergic reactions
- Non-severe allergic reactions such as rash, itching, hives, or swelling of the face
- Myocarditis (inflammation of the heart muscle)
- Pericarditis (inflammation of the lining outside the heart)
- Injection site pain
- Tiredness
- Headache
- Muscle pain
- Chills
- Joint pain
- Fever
- Injection site swelling
- Injection site redness
- Nausea
- Feeling unwell
- Swollen lymph nodes (lymphadenopathy)
- Decreased appetite
- Diarrhea
- Vomiting
- Arm pain
- Fainting in association with injection of the vaccine
- Unusual and persistent irritability
- Unusual and persistent poor feeding
- Unusual and persistent fatigue or lack of energy
- Unusual and persistent cool, pale skin
- Dizziness

These may not be all the possible side effects of these vaccines. Call the vaccination provider or healthcare provider about bothersome side effects or side effects that do not go away.

- Individuals should always ask their healthcare providers for medical advice about adverse events. Report vaccine side effects to the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS). The VAERS toll-free number is 1-800-822-7967 or report online to www.vaers.hhs.gov/reportevent.html . In addition, individuals can report side effects to Pfizer Inc. at www.pfizersafetyreporting.com or by calling 1-800-438-1985

COMIRNATY® Full Prescribing Information and EUA Fact Sheets for Vaccination Providers and Recipients and Caregivers Fact Sheets:

COMIRNATY® Full Prescribing Information (12 years of age and older), DO NOT DILUTE, Gray Cap

EUA Fact Sheet for Vaccination Providers (12 years of age and older), BIVALENT (Original and Omicron BA.4/BA.5), DO NOT DILUTE, Gray Cap

EUA Fact Sheet for Vaccination Providers (5 through 11 years of age), BIVALENT (Original and Omicron BA.4/BA.5), DILUTE BEFORE USE, Orange Cap

EUA Fact Sheet for Vaccination Providers (12 years of age and older), DO NOT DILUTE, Gray Cap

EUA Fact Sheet for Vaccination Providers (5 through 11 years of age), DILUTE BEFORE USE, Orange Cap

EUA Fact Sheet for Vaccination Providers (6 months through 4 years of age), DILUTE BEFORE USE, Maroon Cap

EUA Fact Sheet for Recipients and Caregivers (12 years of age and older)

EUA Fact Sheet for Recipients and Caregivers (5 through 11 years of age)

EUA Fact Sheet for Recipients and Caregivers (6 months through 4 years age)

U.S. FDA EMERGENCY USE AUTHORIZATION STATEMENT
PAXLOVID (nirmatrelvir tablets and ritonavir tablets)

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 pre-exposure or post-exposure prophylaxis for prevention of COVID-19
- PAXLOVID is not authorized for use longer than 5 consecutive days

PAXLOVID may 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.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:
- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

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 Act, 21 U.S.C. 21 § 360bbb-3(b)(1), 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.

Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

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:

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

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 drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- 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. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. 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.

Anaphylaxis and other hypersensitivity reactions have been reported with PAXLOVID. Cases of Toxic Epidermal Necrolysis, and Stevens-Johnson syndrome have been reported with ritonavir, a component of PAXLOVID (refer to NORVIR prescribing information). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

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 of **HIV-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%), 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.

The following adverse reactions have been identified during post-authorization use of PAXLOVID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylaxis and other hypersensitivity reactions
Gastrointestinal Disorders: Abdominal pain, nausea
General Disorders and Administration Site Conditions: Malaise

Required Reporting for Serious Adverse Events and Medication Errors: The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness 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 return 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: http://www.pfizersafetyreporting.com/ or by fax (1-866-635-8337) or phone (1-800-438-1985).

PAXLOVID is a strong 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 CYP3A 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 COVID19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID19.

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**.

Pfizer Contact:
Media Relations
PfizerMediaRelations@pfizer.com

Research

Recent Updates and Statements

01.27.2023 Covid-19 Medicines

Pfizer Receives Positive CHMP Opinion for Conversion of PAXLOVID™ Conditional Marketing Authorization to Full Marketing Authorization in the European Union

01.26.2023 Patient Centricity Responsibility Technology

Data Privacy Day and Our Commitment to You

01.17.2023 Investments

Pfizer to Acquire Sanford, North Carolina Manufacturing Site from Abzena

12.22.2022 Medicines

Hospira, Inc. Issues A Voluntary Nationwide Recall For One Lot of Vancomycin Hydrochloride Injection, USP 1.5g/vial, Due To The Presence of Visible Glass Particulates

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