DATE: January 11, 2022

IMPORTANT PRESCRIBING INFORMATION

Subject: PAXLOVID Emergency Use Authorization (EUA) dosing and dispensing in moderate renal impairment, and risk of serious adverse reactions due to drug interactions

Dear Healthcare Provider,

The purpose of this letter is to make you aware of the EUA dosing and dispensing requirements for patients with moderate renal impairment, and the potential for drug-drug interactions associated with PAXLOVID (nirmatrelvir tablets; ritonavir tablets). PAXLOVID contains two different drugs that are co-packaged in a daily blister card for oral use.

The dosage for PAXLOVID is as follows:

eGFR*	**PAXLOVID Dose**
Greater than 60 mL/min (*normal renal function or mild renal impairment*)	300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
≥30 to <60 mL/min (*moderate renal impairment*)	150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
<30 mL/min (*severe renal impairment*)	PAXLOVID is not recommended (the appropriate dose has not been determined).

*eGFR=estimated glomerular filtration rate based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula

Each daily blister card contains a morning and evening dose, with each dose consisting of 300 mg nirmatrelvir (two oval, pink 150 mg tablets) and 100 mg ritonavir (one ovaloid, white 100 mg tablet) as shown in Figure A below, which is incongruent with the moderate renal impairment dose.

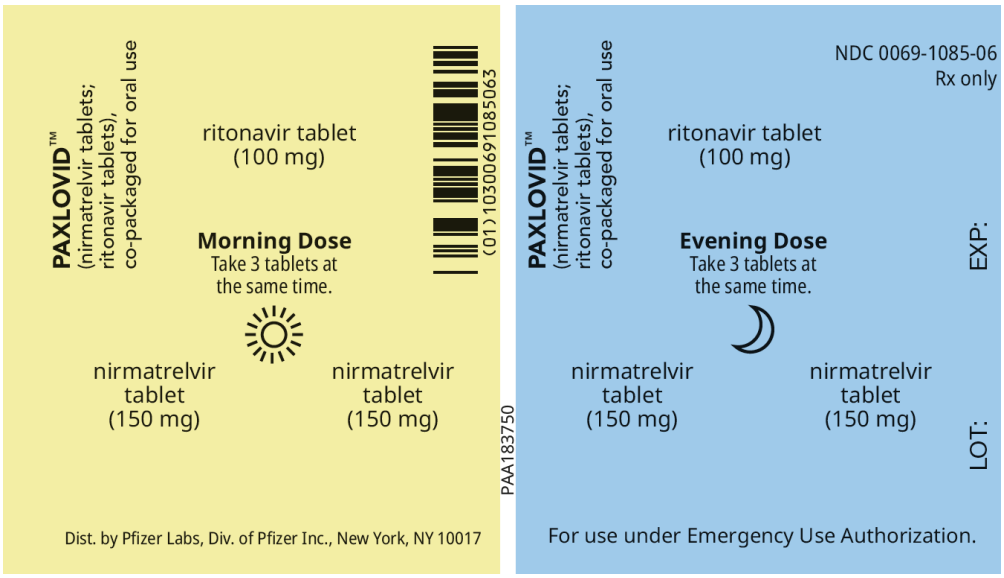

Figure A: Blister card containing morning and evening dose for normal renal function or mild renal impairment

Each daily blister card contains more nirmatrelvir tablets than are needed for dosing in patients with moderate renal impairment. **It is critical that all prescriptions specify the numeric dose for each active ingredient within PAXLOVID as follows:**

- **PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment, or**
- **PAXLOVID 300 mg nirmatrelvir with 100 mg ritonavir for patients with normal renal function or mild renal impairment**

Dispensing information in patients with moderate renal impairment:

Each shipment of PAXLOVID will be accompanied with **instructions, for pharmacists to remove the unneeded, additional nirmatrelvir tablets, and with stickers to affix to each daily blister card as well as the carton** when dispensing PAXLOVID to patients with moderate renal impairment (see below for image of dispensing instructions). **Pharmacists should discard the removed tablets per state requirements or local guidelines.**

Pharmacists should ensure that they refer to the instructions entitled "IMPORTANT PAXLOVID™ DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" regarding specific instructions on tablet removal and proper sticker placement. In addition, **pharmacists should counsel patients** about renal dosing instructions and notify them that their blister cards have been altered at the pharmacy.

IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT

To dispense PAXLOVID dose (150 mg nirmatrelvir with 100 mg ritonavir) for moderate renal impairment, pharmacist should:

STEP ONE: Remove one of the 150 mg nirmatrelvir tablets from the morning dose and remove one of the 150 mg nirmatrelvir tablets from the evening dose of the blister card (see figure 1 below). The nirmatrelvir tablets that are removed should be the ones closest to the middle of the blister pack. Discard the removed tablets per state requirements or local guidelines.

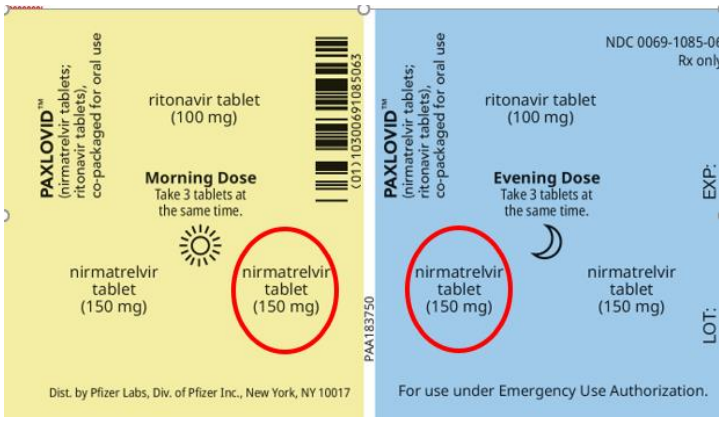

Figure 1: Remove the nirmatrelvir tablets circled in red from the blister card

STEP TWO: Affix the blister card with one sticker from the provided tear pad to carefully cover the empty blister cavities as shown in figure 2 below. The exact placement of this sticker is important to cover the empty blister cavities from the tablets. Ensure the sticker also covers the pre-printed dosing instruction that is on the blister card.

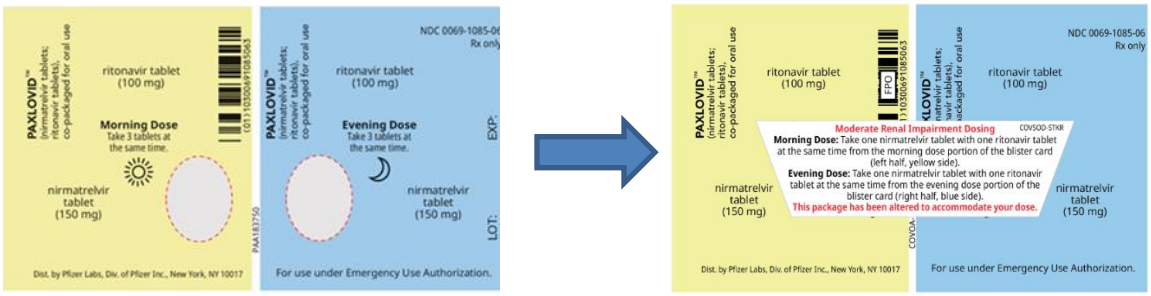

Figure 2: Placement of sticker over empty blister cavities and pre-printed dosing instruction after removal of nirmatrelvir tablets

STEP THREE: Repeat steps one and two for every blister card in the carton (each carton contains five blister cards for a full 5-day dosing regimen).

STEP FOUR: Affix one sticker from the provided tear pad to carefully cover over the pre-printed dosing regimen on the carton as shown in figure 3 below:

Figure 3: Placement of sticker over pre-printed dosing regimen on carton

Patients with moderate renal impairment should be instructed to take only one 150-mg nirmatrelvir tablet with one 100-mg ritonavir tablet together twice daily for 5 days. **Patients with moderate renal impairment should be notified that their blister cards have been altered by their pharmacist to remove unneeded tablets.**

<u>Risk of Serious Adverse Reactions Due to Drug Interactions:</u>

Use of PAXLOVID, a CYP3A inhibitor, in patients receiving concomitant medications metabolized by CYP3A may increase the plasma concentrations of those concomitant medications.

Use of concomitant 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.

See the current EUA 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.

Prescribers and pharmacists should inform patients that PAXLOVID may interact with some drugs and is **contraindicated** for use with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription or non-prescription medication or herbal products.

<u>Indication & Authorized Use:</u>

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.

For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website:

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

Healthcare providers should consider the benefit-risk for an individual patient.

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 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).

Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

Reporting Adverse Events and Medication Errors:

Under the EUA, all serious adverse events and all medication errors potentially related to PAXLOVID must be reported.
Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 (https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 208529787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form. Please provide a copy of all FDA MedWatch forms to Pfizer via fax (1-866-635-8337), telephone (1-800-438-1985) or website www.pfizersafetyreporting.com

The PAXLOVID EUA Fact Sheet for Healthcare Providers is available at www.COVID19oralRx.com or by scanning the QR Code below:

Sincerely,

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