Clinical Pharmacology EUA Summary Review

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Sponsor	Pfizer Inc.
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Drug Name	PAXLOVID (nirmatrelvir oral tablet co-packaged with ritonavir oral tablet)
Dosage and Administration	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days
Indication	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

Rationale for Revisions to EUA Fact Sheets

The PAXLOVID EUA fact sheet was revised as follows:

1. Section 12.3 was edited to include summary data from two additional clinical studies that assessed the role of PAXLOVID as a perpetrator of drug-drug interactions. Study 1013 was a Phase 1, open-Label, 3-Treatment, 6-Sequence, 3-Period crossover study to estimate the effect of PAXLOVID and ritonavir on the pharmacokinetics of midazolam in healthy participants. The three treatment arms in this study included 1) a single oral dose of midazolam 2 mg, 2) multiple oral doses of PAXLOVID 300/100 mg in plus single 2 mg oral dose of midazolam and 3) multiple oral doses of ritonavir 100 + single 2 mg oral dose of midazolam. Midazolam plasma exposure based on geometric mean AUC_{inf} increased approximately 14-fold with a nearly 4-fold increase for C_{max} following co-administration with multiple oral doses of PAXLOVID.

   Study 1012 was a Phase 1, open-label, 3-treatment, 6-Sequence, 3-period crossover study to estimate the effect of PAXLOVID and ritonavir on the pharmacokinetics of dabigatran in healthy participants. Participants in this study received 1) dabigatran etexilate 75 mg as a single dose, 2) PAXLOVID 300 mg/100 mg q12h x 2 days plus 75 mg of dabigatran etexilate as a single dose on Day 2 and 3) Ritonavir 100 mg q12h x 2 days plus 75 mg of dabigatran etexilate as a single dose

on Day 2. Dabigatran plasma exposure based on geometric mean AUC_{inf} and C_{max} increased 1.9-fold and 2.3-fold respectively following co-administration with multiple doses of PAXLOVID.

Based on the results of these studies, we agree with the addition of Table 7 to the factsheet. Edits were also made to Table 2 to reflect that 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and feces, respectively.

2. The following edits were also made to Table 1 in Section 7.3.
    a. Dabigatran was added to the anticoagulants section to state increased dabigatran concentrations when coadministered with PAXLOVID. The clinical pharmacology review team recommended the following clinical comment based on the results of Study 1012 and specific recommendations on dose adjustments in the dabigatran product labeling: *Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information*.

    b. Additional instructions were added to the clinical comments for HMG-CoA reductase inhibitors. For lovastatin and simvastatin, instructions were added to discontinue the use of these statins during the five days of PAXLOVID treatment and for five days after completing PAXLOVID. This language expands on the previous factsheet recommendation to discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.

        The recommendation to discontinue the statin for five days after completion of PAXLOVID is based on the estimated time course of CYP3A recovery after stopping the enzyme inhibitor. In the publication by Stader et al, a modeling approach was used to evaluate the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir[1]. Lopinavir/ritonavir (400/100mg twice daily) was administered for 7 days in a virtual trial to achieve steady state CYP3A inhibition and the abundance of CYP3A was estimated for 21 consecutive days. The interaction potential after stopping lopinavir/ritonavir was investigated with midazolam (a CYP3A probe substrate) administered orally 5mg once daily starting on the seventh day. In all simulations conducted, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/ritonavir. While complete disappearance of CYP3A inhibition took 21 days, the amount of inhibition remaining after five days is not expected to be clinically significant for most drugs.

        In another publication by Hong et al, a physiologically based pharmacokinetic (PBPK) simulation-based approach was applied to predict the effect of ritonavir on the PK of elexacaftor-tezacaftor-ivacaftor (ETI) and determine a potential dose alteration of ETI to overcome the CYP3A inhibition mediated by ritonavir [2]. Steady-state PK of standard dose ETI alone and when co-administered with 100mg ritonavir twice daily for 5 days were

[1] Stader F., et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. Antimicrob Chemother 2020; 75: 3084–3086 doi:10.1093/jac/dkaa253 Advance Access publication 17 June 2020

[2] Hong et al. PBPK-led guidance for cystic fibrosis patients taking elexacaftor-tezacaftor-ivacaftor with nirmatrelvir-ritonavir for the treatment of COVID-19.

simulated. A dose reduction of ETI during 5 days of ritonavir administration with resumption of full dose of ETI on day 9 (4 days after stopping ritonavir) provided a similar steady-state PK profile of the conventional regimen of ETI alone. Based on the data presented in these two studies, the clinical pharmacology review team recommends that patients on lovastatin or simvastatin wait for five days after completing PAXLOVID to resume statin therapy.

For atorvastatin and rosuvastatin, an additional sentence stating the statin does not need to be held prior to or after completing PAXLOVID was added. The Norvir label outlines specific clinical management strategies for these statins.

c. Additional instructions were added to the clinical comment for hormonal contraceptives to instruct patients and providers to consider an additional, non-hormonal method of contraception during the five days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID. This recommendation is based on the potential risk of reduced ethinyl estradiol exposure with ritonavir and is supported by data from the darunavir/ritonavir package insert[3] and a study by Kasserra et al [4], demonstrating a significant decrease in ethinyl estradiol exposure when coadministered with darunavir/ritonavir (600 mg/100 mg) for 14 days or 100 mg ritonavir for 10 days, respectively. While CYP enzymes are likely a contributor to this interaction, there are additional metabolic processes involved in ethinyl estradiol metabolism, including glucuronidation and sulfation. Based on the available data, it is unknown whether the magnitude of enzyme (CYP and non-CYP) induction after five days of PAXLOVID administration would be less compared to that observed with longer ritonavir dosing regimens of 10 to 14 days since the time course of induction of these additional metabolic processes has not been well characterized. Generally, contraceptive efficacy is attributed to progestin more than the estrogen component, however, potential loss of efficacy due to lower ethinyl estradiol exposure cannot be completely ruled out, since efficacy may be affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation, and endometrial lining changes. While the metabolism of progestin also relies on CYP3A, the relative contribution of CYP3A to the clearance of different progestins varies. Other metabolic enzymes, including CYP2C19, uridine 5'-diphospho- glucuronosyltransferases (UGTs), and sulfotransferases (SULTs), are also involved in the metabolism of certain progestins. As previously indicated, , the time course of these additional metabolic processes has not been well characterized.

Clinical Pharmacology Assessment

The review team's recommended revisions, as described above, were accepted by the applicant (with minor editorial revisions). The final agreed upon language is shown below:

[3] PREZISTA [package insert] Janssen Products; 2021.
[4] Kasserra et al. Effect of vicriviroc with or without ritonavir on oral contraceptive pharmacokinetics: a randomized, open-label, parallel-group, fixed-sequence crossover trial in healthy women. Clin Ther. 2011 Oct;33(10):1503-14.

Edits to Table 1 in Section 7.3

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.

Edits to Section 12.3

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00[a]	3.98[a]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7[b]	112.4[b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[b]	13.92[b]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
c. Red blood cell to plasma ratio.
d. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
e. Determined by ^{19}F-NMR analysis following 300 mg oral suspension enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution.

Table 7: Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Co-administered Drug

Co-administered Drug	Dose (Schedule)		N	Percent Ratio of Test/Reference of Geometric Means (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (5 doses)[b]	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentrations.
a. AUC=AUC_{inf} for both midazolam and dabigatran.
b. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=Midazolam. Midazolam is an index substrate for CYP3A4. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=Dabigatran. Dabigatran is an index substrate for P-gp.

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