CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217188
PDUFA Goal Date	May 28, 2023
OSE RCM #	2022-34
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
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Review Completion Date	May 25, 2023
Subject	Determination of the Need for a REMS
Established Name	nirmatrelvir and ritonavir
Trade Name	Paxlovid
Name of Applicant	Pfizer, Inc
Therapeutic Class	Antiviral agent and protease inhibitor
Formulation(s)	nirmatrelvir tablets co-packaged with ritonavir tablets 300 mg/100 mg and 150 mg/100 mg tablets for oral administration
Dosing Regimen	300 mg nirmatrelvir with 100 mg ritonavir with all 3 tablets taken together orally twice daily for 5 days In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of Paxlovid is 150 mg nirmatrelvir and 100 mg ritonavir with both tablets taken together twice daily for 5 days

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Paxlovid (nirmatrelvir and ritonavir), is necessary to ensure the benefits outweigh its risks. Pfizer, Inc submitted a New Drug Application (NDA) 217288 for Paxlovid with the proposed indication: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death. The FDA approved indication will be for the treatment of mild-to-moderate coronavirus 2019 (COVID-19) in adults who are at risk for progression to severe COVID-19, including hospitalization or death. The key safety concern determined to be associated with Paxlovid is the risk of serious adverse reactions due to drug-drug interactions (DDIs). The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Antivirals (DAV) have determined that a REMS is not needed to ensure the benefits of Paxlovid outweigh its risks. The risk of serious adverse reactions due to DDIs, mainly due to the ritonavir component, will be addressed in labeling with a Boxed Warning. The Boxed Warning states to review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like Paxlovid, and to determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. Additionally, the label includes a table listing the clinically significant drug interactions, including contraindicated drugs for Paxlovid (not comprehensive) in Section 7.3, "Established and Other Potentially Signification Drug Interactions." This table includes a "Clinical Comments" column which provides guidance for the prescriber and patient to determine how to proceed with certain drug-drug combinations. Overall, the available safety data from the clinical trials demonstrate that Paxlovid is safe for its intended use and the risk of serious adverse reactions due to DDIs can be mitigated through labeling and further evaluated during routine pharmacovigilance.

1 Introduction

This review evaluates whether a REMS for the NME, Paxlovid (nirmatrelvir and ritonavir) is necessary to ensure the benefits outweigh its risks.[a] Pfizer, Inc submitted NDA 217188 for nirmatrelvir and ritonavir with the proposed indication: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.[1] This application is under review in the Division of Antivirals (DAV). The Applicant did not submit a proposed REMS or risk management plan with this application.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2 Background

2.1 PRODUCT INFORMATION

Paxlovid, an NME, includes nirmatrelvir (peptidomimetic inhibitor of the severe acute respiratory syndrome coronavirus 2 main protease inhibitor [SARS-CoV-2 M^{pro}]) co-packaged with ritonavir (HIV-1 protease inhibitor and CYP3A inhibitor). Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication. Ritonavir inhibits the Cytochrome P450 3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

The proposed indication for Paxlovid is for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.[1,2]

The FDA approved indication will be:[2]
Paxlovid is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID 19, including hospitalization or death.

Paxlovid is available as nirmatrelvir 150 mg tablets and co-packaged with 100 mg tablets of ritonavir. The proposed dose of Paxlovid is 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg of ritonavir (one 100 mg tablet), with all 3 tablets taken by mouth together twice daily for 5 days. There is a 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.

Ritonavir has been approved in the US since 1996 in various formulations including tablets and oral solution and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The oral powder formulation is indicated for the treatment of pediatric patients with HIV-1 infection.[3] Ritonavir is approved with a Boxed Warning for drug-drug interactions (DDIs) leading to potentially serious and/or life-threatening reactions. The proposed label for Paxlovid also includes a Boxed Warning for DDIs.[2]

Paxlovid is not currently approved in any jurisdiction, however, on December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) for emergency use of PAXLOVID 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.[4]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 217188 relevant to this review:

- **12/22/2020**: Pfizer, Inc submitted IND 153517 for PF-07321332 for the treatment of COVID-19.
- **10/21/2021**: Pfizer, Inc submitted an Emergency Use Authorization (EUA) request for Paxlovid for the treatment of mild-moderate COVID-19.

- **12/22/2021**: The FDA issued an EUA for Paxlovid 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, including hospitalization or death based on the totality of scientific evidence available to the Agency, including data from the clinical trial EPIC-HR (NCT04960202), a phase 2/3 randomized, double blind, placebo-controlled clinical trial.
- **02/17/2022**: Fast Track Designation was granted for Paxlovid for the treatment of COVID-19.
- **06/29/2022**: Pfizer, Inc submitted NDA 217188 for Paxlovid for the following proposed indication: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.
- **10/27/2022**: A Post Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency does not anticipate a REMS will be needed.
- **12/16/2022**: The Applicant's submissions on November 23, 2022, and December 5, 2022, constituted a major amendment to NDA 217188. The goal date was extended by three months. The extended user fee goal date is May 28, 2023.
- **03/16/2023**: The Antimicrobial Drugs Advisory Committee (AMDAC) meeting convened to discuss Paxlovid. The majority of the committee voted "yes" (16/17) for to the question, "Is the overall benefit-risk assessment favorable for Paxlovid when used for the treatment of mild to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?"

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

At the end of 2019, a novel coronavirus, SARS-CoV-2, was identified which resulted in a world-wide pandemic. SARS-CoV-2, commonly referred to as COVID-19, is a serious and potentially life-threatening illness, which can result in pneumonia, multiorgan failure, respiratory failure, and death.[5] Patients may experience the following symptoms: fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste and smell.[6] Some patients may also experience "long COVID" or "post-COVID conditions" which includes a broad range of symptoms (physical and mental) and symptom clusters that develop during or after COVID-19, continue for ≥2 months (i.e., three months from the onset of illness), have an impact on the patient's life, and are not explained by an alternative diagnosis.[7] As of March 10, 2023, there have been over 100 million cases of COVID-19 infection with approximately 1.1 million deaths attributable to COVID-19 in the United States.[8]

Table 1:[6] Clinical Spectrum of COVID-19 Infection

COVID-19 Severity	Definition
Asymptomatic or Pre-symptomatic	Test positive using a virologic test but have no symptoms
Mild	Presence of symptoms without shortness of breath or abnormal chest imaging
Moderate	Presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥ 94% on room air
Severe	Oxygen saturation < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of < 300 mmHg, a respiratory rate > 30 breaths/minute, or lung infiltrates > 50%
Critical	Respiratory failure, septic shock, and/or multiorgan dysfunction

3.2 Description of Current Treatment Options

Non-pharmacologic treatment of COVID-19 includes supportive care and convalescent plasma. Convalescent plasma is obtained from individuals, usually by apheresis, who have recovered from an infection and have generated an immune response against the infective pathogen. During the COVID-19 pandemic, over 250,000 units have been administered to patients via an expanded access program, emergency use authorizations, and clinical trials. The risk of serious adverse events associated with convalescent plasma for COVID-19 are low.[9] However, it is no longer widely available.

Remdesivir (Veklury), administered by intravenous infusion daily for 3 days, is the only FDA-approved treatment option for COVID-19. It is indicated for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are: hospitalized or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[10] However, access to remdesivir may be difficult for non-hospitalized patients as it requires a health care facility that can administer infusions and should be initiated within 7 days of symptom onset.

The FDA issued an Emergency Use Authorization (EUA) for both Paxlovid and Lagevrio (molnupiravir) on December 22, 2021, and December 23, 2021, respectively. Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. It is authorized for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19): who are at high risk for progression to severe COVID-19, including hospitalization or death; and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.[11] The National Institutes of Health guidelines offer molnupiravir as an alternative to those who cannot receive Paxlovid and remdesivir.[12] Anti-SARS-CoV-2 therapeutic monoclonal antibodies (mAbs) were previously available under EUA for the treatment of mild-to-moderate COVID-19 in certain individuals at high risk for progression to severe disease. However, no anti-SARS-CoV-2 mAbs are currently authorized for emergency use for COVID-19 treatment due to nonsusceptibility to the currently circulating SARS-CoV-2 Omicron subvariants.

There is an unmet medical need for safe, effective, and convenient outpatient COVID-19 treatment options, particularly ones with a target that is anticipated to be conserved across the different SARS-CoV-2 variants and subvariants.[13]

4 Benefit Assessment

4.1 EPIC-HR

EPIC-HR or C4671005 (NCT 04960202) is the pivotal, Phase 2/3, randomized, double-blind, placebo-controlled trial that provides the primary basis of efficacy and safety of nirmatrelvir/ritonavir for treatment in patients with mild-to-moderate COVID-19 who were at high risk for progression to severe COVID-19, including hospitalization or death.

Participants with a confirmed diagnosis of SARS-CoV-2 infection and with symptom onset within five days were randomized 1:1 to receive nirmatrelvir 300 mg co-administered with ritonavir 100 mg (N = 1,049) or placebo (N = 1,064) orally every 12 hours for five days (10 doses in total). The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 in the modified intent to treat (mITT) population. The first key secondary efficacy endpoint was proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 in mITT1 population. The second key secondary efficacy endpoint was time to sustained alleviation of all targeted signs/symptoms through Day 28 in mITT.

The proposed label focuses on the MITT1 population. Results showed there was a 5.6% absolute reduction (95% confidence interval [CI]: -7.3% to -4.0%; p<0.0001) or 86% relative reduction (95% CI: 72%, 93%), compared to placebo, for the primary efficacy endpoint of COVID-19 related hospitalization or death from any cause through Day 28 in the mITT1 population. Refer to the tables below for details.

Table 2:[5] Proportion of Participants with COVID-19-Related-Hospitalization or Death from Any Cause Through Day 28, Trial EPIC-HR

mITT: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤ 3 days of COVID-19 symptom onset		
	Paxlovid N=671	**Placebo N=647**
Participants with event, n (%)	5 (0.7)	44 (6.8)
COVID-19 hospitalization	5 (0.7)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[a]	-6.1 (-8.2, -4.1)	
Two-sided p-value	<0.0001	
mITT1: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were dosed ≤ 5 days of COVID-19 symptom onset		
	Paxlovid N=977	**Placebo N=989**
Participants with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)

Estimated difference in proportion % (95% CI)[a]	-5.6 (-7.3, -4.0)	
Two-sided p-value	<0.0001	
mITT2: All participants randomly assigned to study intervention who took at least 1 dose of study intervention and were dosed ≤ 5 days of COVID-19 symptom onset		
	Paxlovid N=1038	**Placebo N=1053**
Participants with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[a]	-5.4 (-7.0, -3.8)	
Two-sided p-value	<0.0001	
mAb = monoclonal antibody		

Table 3:[5] Time to Sustained Symptom Resolution through Day 28, Trial EPIC-HR in the mITT

	Paxlovid N=666	**Placebo N=645**
Participants with sustained symptom resolution, n (%)	445 (66.8)	388 (60.2)
Median time to sustained symptom resolution by Day 28 (95% CI)	16 (14, 17)	18 (17, 20)
Two-sided p-value	0.0026	

4.2 EPIC-SR

EPIC-SR (C4671002 – NCT 05011513) was a randomized, double-blind, global trial in which non-hospitalized adults who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated with no risk factors for progression to severe disease were randomized to receive 5 days of PAXLOVID versus placebo for the treatment of mild-to-moderate COVID-19. A total of 1,075 patients were randomized (1:1) to receive Paxlovid or placebo orally every 12 hours for 5 days; of these, 59% were fully vaccinated and high-risk.[2]

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met. In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.[2]

The clinical review team concluded that the clinical trial results from EPIC-HR and EPIC-SR support the efficacy of Paxlovid for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. Although the clinical trial data was limited to assess efficacy against the Omicron variant, the clinical reviewer concluded that Paxlovid is likely to retain clinical efficacy against the currently circulating Omicron subvariants.[13]

(b) (4)

(b) (4)

5 Risk Assessment & Safe-Use Conditions

The safety of Paxlovid was established in two Phase 2/3 randomized, placebo-controlled trials in symptomatic adult subjects 18 years of age and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection, EPIC-HR and EPIC-SR. In comparison, EPIC-HR included patients (Paxlovid – N = 1,038; Placebo – N = 1,053) who were at high risk for progression to severe disease while EPIC-SR enrolled patients (Paxlovid – N = 540; Placebo – N = 528) who were at standard risk for progression to severe disease (previously unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease).[5] Adverse reactions were those reported while patients were on study medication and through 28 days after the last dose of study treatment.

In EPIC-HR, the most common adverse reactions (≥ 1% incidence in the Paxlovid group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively). In EPIC-SR, the adverse reactions observed were consistent with those observed in EPIC-HR.[2] Overall, no deaths occurred in patients who received Paxlovid.

The following adverse reactions have been identified during use of Paxlovid under EUA:[2]

- *Immune System Disorders:* Anaphylaxis, hypersensitivity reactions
- *Skin and Subcutaneous Tissue Disorders:* Toxic Epidermal Necrolysis, Stevens-Johnson syndrome
- *Nervous System Disorders:* Headache
- *Vascular Disorders:* Hypertension
- *Gastrointestinal Disorders:* Abdominal pain, nausea, vomiting
- *General Disorders and Administration Site Conditions:* Malaise

The key safety concern determined to be associated with Paxlovid is the risk of serious adverse reactions due to drug-drug interactions (DDIs).[b]

5.1 Drug-Drug Interactions

Ritonavir, a component of Paxlovid, exhibits strong Cytochrome P450 3A (CYP3A) inhibition and can result in significant elevations of concomitant medications that are metabolized by CYP3A. Both EPIC-HR and EPIC-SR excluded patients with current or expected use of any medications that have DDIs with Paxlovid; therefore, this risk could not be evaluated in those studies. However, analyses of post-EUA data shows:[13]

- Over 50% of Paxlovid-eligible patients (adults who are at high risk for development of severe COVID-19) are on medications with DDIs with Paxlovid.
- The majority of Paxlovid prescribers are adult primary care practitioners.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

- Serious adverse reactions, including death, have been reported in association with DDIs that are included in the current EUA Fact Sheet for Healthcare Providers. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and calcium channel blockers.

The clinical review team concluded based on the safety surveillance data this information should be highlighted in the prescribing information using a Boxed Warning.

The proposed Boxed Warning is as follows:[2]

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*
- Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].*
- Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].*

A table listing of the clinically significant drug interactions, including contraindicated drugs for Paxlovid (not comprehensive) is provided in Section 7.3, "Established and Other Potentially Signification Drug Interactions," of the proposed label.[2] This table includes a "Clinical Comments" column which provides guidance for the healthcare provider and patient to determine how to proceed with certain drug-drug combinations.

5.2 HYPERSENSITIVITY REACTIONS

Anaphylaxis, serious skin reactions (including Toxic Epidermal Necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with Paxlovid.[2] In EPIC-HR, the frequency of hypersensitivity events were 0.4% in the Paxlovid group and 0.5% in the placebo group. In EPIC-SR, hypersensitivity events were 0.4% in the placebo group and none in the placebo group. There were no deaths or serious adverse events or deaths related to hypersensitivity events. There were no cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, or anaphylaxis reported in either EPIC-HR or EPIC-SR.[13]

The proposed label includes a Warning and Precaution for hypersensitivity reactions that states,[2] "If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care."

6 Expected Postmarket Use

If approved, Paxlovid will primarily be used in the outpatient setting. The likely prescribers will be adult primary care providers. These providers may not be as familiar with managing ritonavir DDIs as

providers who specialize in HIV management. However, the proposed Paxlovid label states, "Prior to prescribing PAXLOVID, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring." The label also refers prescribers to view the table of clinically significant drug interactions, including contraindicated drugs as a guide to drug therapy management. This information was also provided in the Fact Sheet for Healthcare Providers: EUA for Paxlovid.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Paxlovid beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA review team has determined, based upon review of all available efficacy and safety data, the benefits of Paxlovid outweigh the risks for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe disease.[13]

COVID-19 is a serious and potentially life-threatening illness with a clinical spectrum that varies greatly. As of March 10, 2023, there have been over 100 million cases of COVID-19 infection with approximately 1.1 million deaths attributable to COVID-19 in the United States. There is an unmet medical need for safe, effective, and convenient outpatient COVID-19 treatment options, particularly ones with a target that is anticipated to be conserved across the different SARS-CoV-2 variants and subvariants.[13]

The key safety concern with Paxlovid is the risk of serious adverse reactions due to DDIs. While primary care provides may not be as familiar with managing DDIs with ritonavir as other specialists, many of the DDIs can be managed by dose adjustment, interruption, and/or additional monitoring of the concomitant medication. Prescribers need to consider the benefit of Paxlovid treatment in reducing hospitalization and death versus the risk of potential DDIs for an individual patient. This risk is described in Paxlovid's proposed labeling with a Boxed Warning to highlight this important risk.[13] The proposed label also includes a table of clinically significant drug interactions, including contraindicated drugs, as a guide to drug therapy management. Additionally, other CYP 3A4 inhibitors like clarithromycin and voriconazole have DDIs addressed in "Section 7 – Drug Interactions" of their respective labeling. Overall, the available safety data from the clinical trials demonstrate that Paxlovid is safe for its intended use and the risk of serious adverse reactions due to DDIs can be mitigated through labeling and further evaluated during routine pharmacovigilance.[13]

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Paxlovid to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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