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LORLATINIB® (lorlatinib) Use with PAXLOVID® (nirmatrelvir/ritonavir)

Please refer to the full Prescribing Information on important treatment considerations for LORBRENA® (lorlatinib), via the following link: Lorbrena USPI. In the event this link does not work, please access the product's approved Prescribing Information at https://www.pfizer.com/. Note: select prescribing information is excerpted further in the document.

SUMMARY

- When considering drug combinations, the pharmacokinetics, pharmacodynamics, and safety profiles for each medication may be considered to help identify potential sources of interaction. Pfizer has not conducted any studies evaluating the safety and efficacy of lorlatinib in combination with nirmatrelvir/ritonavir. For this reason, Pfizer cannot make any recommendations concerning their use in combination. Healthcare providers may consider the information below and in the Prescribing Information in determining if the combination of nirmatrelvir/ritonavir with lorlatinib is suitable for patient use.
- Avoid concomitant use of lorlatinib with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor is unavoidable, reduce the starting dose of lorlatinib. [1]
- Lorlatinib is a moderate CYP3A inducer. Concomitant use of lorlatinib decreases the concentration of CYP3A substrates, which may reduce the efficacy of these substrates. [1]
- Initiation of nirmatrelvir/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving nirmatrelvir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir/ritonavir, respectively. [2]
- Nirmatrelvir/ritonavir efficacy and safety data specific for patients with cancer, namely in lorlatinib-treated patients, are not available. [2]
- Information regarding potential interactions between nirmatrelvir/ritonavir and lorlatinib may be available at the Liverpool COVID-19 Drug Interactions website, which can be accessed at: https://www.covid19-druginteractions.org/checker[5]
- EPIC-HR (C4671005) Phase 2/3 clinical study enrolled participants with at least 1 medical condition or risk factor associated with developing severe coronavirus disease 2019 (COVID-19) illness, including participants receiving cancer chemotherapy within 90 days prior to study entry or had active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment was not among the prohibited medications that had to be administered/continued during the trial period. Anticancer drugs were permitted to be used with caution and required oversight by the investigator when co-administered with nirmatrelvir/ritonavir.[3]
- Pfizer is unable to make specific recommendations for individual patients, regarding management or monitoring of potential interactions when combining nirmatrelvir/ritonavir with lorlatinib or when to stop/restart lorlatinib before/after treatment with nirmatrelvir/ritonavir. Clinical judgment based on the medical history and the clinical status of a specific patient should dictate the appropriate actions to be taken.
- This letter regarding lorlatinib and nirmatrelvir/ritonavir includes information for which the products are not approved and/or inconsistent with the product uses described in the Prescribing Information. Pfizer does not suggest or recommend its use in any manner other than as described in the Prescribing Information.

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As these medications may share some similar adverse events (AEs), it is possible that these events become additive if these drugs are administered concomitantly. A few of these AEs are listed below. Please consult the respective Prescribing Information of nirmatrelvir/ritonavir and labelling for lorlatinib for information on listed interactions and their treatment-emergent AEs.

Nirmatrelvir/ritonavir analysis of data specific for cancer patients, namely in lorlatinib-treated patients, are not available.

LORLATINIB Prescribing Information[1]

Drug Interactions

Concomitant use with a strong CYP3A inhibitor increased lorlatinib plasma concentrations, which may increase the incidence and severity of adverse reactions of lorlatinib. Avoid concomitant use of lorlatinib with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce the lorlatinib dosage.[1]

Lorlatinib is a moderate CYP3A inducer. Concomitant use of lorlatinib decreases the concentration of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of lorlatinib with certain CYP3A substrates, for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling. [1]

Dosage Modification for Strong CYP3A Inhibitors

Avoid concomitant use of lorlatinib with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor is unavoidable, reduce the starting dose of lorlatinib from 100 mg orally once daily to 75 mg orally once daily. [1]

In patients who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce the lorlatinib dose to 50 mg orally once daily. [1]

If concomitant use of a strong CYP3A inhibitor is discontinued, increase the lorlatinib dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor. [1]

PAXLOVID Prescribing Information[2]

Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of Paxlovid (nirmatrelvir co-packaged with ritonavir), a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving nirmatrelvir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A.[2]

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir/ritonavir, respectively. [2]

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications. [2]
- Clinically significant adverse reactions from greater exposures of nirmatrelvir/ritonavir. [2]
- Loss of therapeutic effect of nirmatrelvir/ritonavir and possible development of viral resistance. [2]

Potential for Nirmatrelvir/Ritonavir to Affect Other Drugs

Nirmatrelvir/ritonavir is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of nirmatrelvir/ritonavir 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. Please refer to Table 1 in the Prescribing Information. [2]

Potential for Other Drugs to Affect Nirmatrelvir/Ritonavir

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce nirmatrelvir/ritonavir therapeutic effect. [2]

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For further information regarding indications, dosage & administration, contraindications, warnings & precautions, interactions, and adverse effects, please refer to the full Prescribing Information for Paxlovid and Lorbrena.

LITERATURE SEARCH

As of May 10, 2022, a search of the published medical literature has failed to identify any clinical publications discussing the concomitant use of lorlatinib and nirmatrelvir/ritonavir (PF-07321332; ritonavir). However, we are aware of some unpublished data regarding use of nirmatrelvir/ritonavir in patients with cancer. A review of this data is summarized in the Clinical Data section below. The search is subject to the inherent limitations of database searching and cannot be considered exhaustive.

INTRODUCTION

When considering drug combinations, pharmacokinetic, pharmacodynamics, and safety profiles for each medication, in this case, lorlatinib and nirmatrelvir/ritonavir, may be considered to help identify potential sources of interaction. Pfizer has not conducted any studies evaluating the safety and efficacy of lorlatinib in combination with nirmatrelvir/ritonavir. Healthcare providers may consider the information below and in the Prescribing Information in determining if the combination of nirmatrelvir/ritonavir with lorlatinib is suitable for patient use.

A non-exhaustive list of drug interactions is provided in the Prescribing Information of nirmatrelvir/ritonavir. If a drug is not listed in the Prescribing Information or in this letter, it should not be assumed it is safe to co-administer with nirmatrelvir/ritonavir in patients. Please consult the respective Prescribing Information of lorlatinib and nirmatrelvir/ritonavir for information on listed interactions and treatment-emergent adverse events.

CLINICAL DATA

The concomitant use of lorlatinib and nirmatrelvir/ritonavir has not been assessed.

Paxlovid (nirmatrelvir/ritonavir) Data

EPIC-HR (High Risk) Study (C4671005); [ClinicalTrials.gov Identifier: NCT04960202]

The EPIC-HR Phase 2/3, double-blind 2-arm study evaluated the efficacy and safety of nirmatrelvir/ritonavir for the treatment of non-hospitalized, symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe disease. Subjects eligible to participate included those having at least 1 medical condition or risk factor associated with developing severe COVID-19 illness. Medical conditions included participants who were receiving cancer chemotherapy within 90 days prior to study entry or had active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment was not among the prohibited medications that had to be administered/continued during the trial period.[3]

During the EPIC-HR clinical study, concomitant use of any medications or substances that are strong inducers of CYP3A4 were prohibited within 28 days prior to first dose of nirmatrelvir/ritonavir and during study treatment.[3]

Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events were not permitted during dosing of nirmatrelvir/ritonavir (at least 24 hours prior to the first dose of study intervention or as late as Day 1, prior to the first dose of study intervention) and for 4 days after the last dose of nirmatrelvir/ritonavir. If a participant cannot temporarily interrupt the prohibited medication during this period, they should be considered ineligible.[3]

In this trial, 8 (0.7%) and 11 (1.0%) patients enrolled, respectively, in the nirmatrelvir/ritonavir and placebo arm received concomitantly antineoplastic agents, however, none received concomitantly lorlatinib.[4]

Pfizer has no additional information to share regarding efficacy or safety data specific for nirmatrelvir/ritonavir use in patients with cancer/receiving anticancer medicines other than that outlined in the Prescribing Information.

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Note that Pfizer is independent of these drug interaction checkers.

Information regarding potential interactions between nirmatrelvir/ritonavir and a specific anticancer drug might be available at the Liverpool COVID-19 Drug Interactions website which can be accessed at: https://www.covid19-druginteractions.org/checker.[5]

The interaction database Micromedex indicates a theoretical major interaction between lorlatinib and nirmatrelvir/ritonavir, as both nirmatrelvir and ritonavir are substrates of CYP3A4, nirmatrelvir is a possible CYP3A4 inhibitor and ritonavir is a CYP3A inhibitor.[6]

The Stockley's Drug Interactions handbook indicated a severe, theoretical, systemic interaction between lorlatinib and ritonavir, as ritonavir is predicted to increase the exposure to lorlatinib. The database indicates that if the concurrent use is unavoidable, the lorlatinib dose should be decreased to 75 mg (or to 50 mg if patient is already on 75 mg) once daily. Once ritonavir is stopped for 3 to 5 half lives, the lorlatinib dose should be increased to the dose used before starting ritonavir.[7]

The database Epocrates indicates that the combined use of ritonavir and lorlatinib should be avoided and alternatives should be selected. Nirmatrelvir and ritonavir levels and efficacy may decrease. An increase of lorlatinib levels was suggested and an increased risk of PR prolongation, cardiac arrhythmias, AV block, and other AEs.[8]

The Drug Interaction Checker indicates a major interaction between lorlatinib and ritonavir, as coadministration with potent CYP3A4 inhibitors may increase lorlatinib's plasmatic concentration and the risk of serious side effects. Also, lorlatinib may reduce the blood levels of nirmatrelvir and may make nirmatrelvir less effective in treating COVID-19 infection in some cases. Response to antiviral treatment should be closely monitored when a CYP450 3A4 inducer is added to or withdrawn from therapy.[9]

The standard interaction database Medscape indicates a serious interaction between lorlatinib and nirmatrelvir/ritonavir and the concomitant administration should be avoided or an alternate drug should be opted. By affecting hepatic/intestinal enzyme CYP3A4 metabolism, lorlatinib may decrease the level or effect of ritonavir, and ritonavir may increase the level or effect of lorlatinib. If unavoidable, the lorlatinib dose should be reduced by 25 mg/day and re-increase to previous dose if ritonavir is discontinued (after 3 plasma half-lives of ritonavir). [10]

The healthcare provider should consult appropriate references for comprehensive information.

Pfizer is unable to make any specific recommendations for individual patients, regarding management or monitoring of potential interactions when combining nirmatrelvir/ritonavir with lorlatinib or when to stop/restart lorlatinib before/after treatment with nirmatrelvir/ritonavir. Clinical judgement based on the medical history and the clinical status of a specific patient should dictate the appropriate actions to be taken.

REFERENCES

1 LORLATINIB (lorlatinib) US Prescribing Information. Pfizer.
2 PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) Emergency Use Authorization Fact Sheet for Healthcare Providers. Pfizer.
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