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Report on Investigation Results

December 22, 2025

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	a. Riociguat
	b. Ensitrelvir fumaric acid
	c. Lonafarnib
[Brand name]	See Appendix 1.
[Marketing authorization holder]	See Appendix 1.
[Indications]	See Appendix 1.
[Dosage and administration]	See Appendix 1.
[Investigating office]	Office of Pharmacovigilance I
	Office of Pharmacovigilance II

II. Investigation background

Riociguat (brand name: Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg) was approved for marketing in Japan on January 17, 2014, for the indication of treatment of “inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or postoperative persistent or recurrent CTEPH.” On February 20, 2015, the partial change application to add the indication of “pulmonary arterial hypertension” (hereinafter referred to as “PAH”) was approved.

For ensitrelvir fumaric acid (hereinafter referred to as “ensitrelvir”) and lonafarnib, concomitant use of these drugs with riociguat has been contraindicated since the marketing approval in November 2022 and January 2024, respectively, by referring to other strong CYP3A inhibitors, for the reason that these drugs are strong CYP3A inhibitors (See III.1).

In April 2024, a consultation associated with the revision of a package insert was requested by the marketing authorization holder (hereinafter referred to as MAH) of riociguat, who intended to revise the package insert, etc. as follows: For co-administration with ensitrelvir, on the basis of the results of clinical trials investigating the pharmacokinetic drug-drug interactions between riociguat and anti-HIV drugs including HIV proteases inhibitors, as well as in vitro studies, riociguat was found to be metabolized mainly by CYP1A1; therefore, the

contraindications for co-administration of riociguat with ensitrelvir specified with reference to other strong CYP3A inhibitors were not appropriate and co-administration with ensitrelvir should be specified in the Precautions for Co-administration section. In response to the consultation, in addition to ensitrelvir for which the consultation was held, the PMDA decided to conduct an investigation on the necessity of re-evaluating the relevant contraindication for co-administrations with itraconazole, voriconazole, and lonafarnib, for which contraindications for co-administration with riociguat are listed with consideration given to the inhibitory effects of CYP isoforms including CYP3A. In its deliberation meeting held on April 25, 2025, the, Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Council concluded that contraindications for co-administration with itraconazole and voriconazole may be lifted on the condition that measures to minimize a risk of hypotension, etc. associated with increased exposure to riociguat by their interactions be taken. For ensitrelvir and lonafarnib, on the other hand, the deliberation was left open because it is difficult to determine whether these drugs inhibit CYP1A1 and to what extent the drugs inhibit it. Therefore, it was decided to deliberate on it again after the results of studies, including in vitro studies to confirm the inhibitory activity of these drugs against CYP1A1, are submitted[1].

For this investigation, the MAH of riociguat submitted results from in vitro studies to characterize inhibition of ensitrelvir and lonafarnib against CYP1A1. In response to the submission, PMDA performed an investigation again to determine whether the contraindications for co-administration need to be reviewed.

The PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Outline of investigation by the PMDA

1. Pharmacokinetics

The MAH of riociguat explained that CYP1A1 is involved mainly in the metabolism of riociguat to its main metabolite M1, and CYP3A4 is partly involved in it, based on the materials submitted at the initial approval review of riociguat and the review of

[1] Report on Deliberation Results
(https://www.pmda.go.jp/files/000275443.pdf)

contraindications for co-administration with HIV protease inhibitors. The MAH of riociguat also explained as follows: Riociguat is a substrate of P-gp and BCRP; however, the effect on the pharmacokinetics of riociguat by inhibition of P-gp and BCRP in the kidney and the digestive tract is considered to be limited.

For ensitrelvir and lonafarnib, the material submitted at the time of the approval review reported the following: A clinical drug-drug interaction study was conducted for ensitrelvir and lonafarnib, respectively, in which midazolam, an index drug of CYP3A substrates, was concomitantly used; the study results revealed that AUC of midazolam was 6.77-fold and 7.39-fold when co-administered with ensitrelvir and lonafarnib, respectively, compared to that for midazolam alone.[2]

In addition, for the review of contraindications for co-administration in this investigation, the results of an in vitro study regarding drug-drug interaction of riociguat with ensitrelvir or lonafarnib (Study KINM 250068-ELB) were submitted by the MAH of riociguat.

1.1 In vitro study regarding the drug-drug interaction of riociguat with ensitrelvir or lonafarnib (Study KINM 250068-ELB)

An in vitro study was conducted to evaluate the inhibitory activity of ensitrelvir and lonafarnib against the metabolism of riociguat via CYP1A1 and CYP3A4 and to estimate the effect on the exposure to riociguat when these drugs are co-administered with riociguat. In this study, ketoconazole and clarithromycin were used as positive controls.

By incubating riociguat with recombinant human CYP1A1 or CYP3A4 (20 minutes for CYP1A1, 60 minutes for CYP3A4) in the presence or absence of ensitrelvir, lonafarnib, ketoconazole, or clarithromycin and by measuring the concentrations of M-1, the main metabolite of riociguat, the concentration of each drug required for 50% inhibition of CYP1A1 or CYP3A4 (hereinafter referred to as "IC_{50}") and the inhibition constant (hereinafter referred to as "Ki value") were calculated. In addition, based on the Ki values and the in vivo concentration of each drug as well as estimated fractions[3] metabolized of riociguat for CYP1A1 and CYP3A4, the ratio of AUC of riociguat when co-administered with each drug

[2] Review report of ensitrelvir (https://www.pmda.go.jp/drugs/2022/P20220719001/340018000_30400AMX00205000_A100_4.pdf) (in Japanese), (https://www.pmda.go.jp/files/000249828.pdf) (in English)
Review report of lonafarnib (https://www.pmda.go.jp/drugs/2024/P20240116001/111298000_30600AMX00019_A100_1.pdf) (only in Japanese)

[3] The estimated fractions metabolized were calculated by the data including the results of human mass-balance studies and clinical drug-drug interaction studies (estimated fractions metabolized of riociguat: 0.0 to 0.65 for CYP1A1, and 0.20 to 0.40 for CYP3A4).

compared to that of administered alone in vivo was estimated[4].

In this study, IC_{50} values against CYP1A1 for ensitrelvir, lonafarnib, ketoconazole, and clarithromycin were 41 μmol/L, 8.6 μmol/L, 0.021 μmol/L, and >100 μmol/L, respectively. IC_{50} values against CYP3A4 for ensitrelvir, lonafarnib, ketoconazole, and clarithromycin were 0.18 μmol/L, 0.92 μmol/L, 0.065 μmol/L, and 1.6 μmol/L, respectively.

The AUC ratios of riociguat in co-admiration with each active ingredient compared to that of riociguat alone estimated from this study were 1.22 to 1.62 for ensitrelvir, 1.10 to 1.24 for lonafarnib, 1.30 to 3.54 for ketoconazole, and 1.17 to 1.40 for clarithromycin.

The ranges of AUC ratios of riociguat in co-administration with ketoconazole or clarithromycin estimated from this study were similar to those of co-administration with ketoconazole or clarithromycin in the clinical drug-drug interaction study (2.50 [90% CI: 2.14−2.92] in co-administration with ketoconazole, 1.41 [90% CI: 1.23−1.63] in co-administration with clarithromycin) (Study 11261 and Study 13284) submitted at the time of the initial approval review of riociguat.

The MAH of riociguat explained that ensitrelvir and lonafarnib are expected to impact the riociguat exposure to an extent comparable to that of clarithromycin, when riociguat is co-administered with ensitrelvir or lonafarnib in clinical settings.

2. Safety

2.1 Adverse event/adverse reaction case reports

Cases reported in Japan or overseas in which riociguat was co-administered with ensitrelvir or lonafarnib were retrieved from the safety database of the MAH of riociguat and had no adverse reaction cases (Date of data lock: End of September 2025).

2.2 Published literature

The MAHs of the investigated inhibitors searched for published literature[5] on safety and pharmacokinetic impacts regarding the co-administration of riociguat with ensitrelvir or lonafarnib but identified no relevant published literature.

[4] As for the estimation method of AUC ratios, the existing report (Clin Pharmacokinet 2007:46:681-696, AAPS J 2014:16:1309-1320) was referred to.

[5] Each of the MAHs of riociguat and the investigated inhibitors searched for published literature on co-administration of riociguat and the investigated inhibitors (including their non-proprietary names) using Embase, PubMed, the MAH's database, etc.(Search date: November 3, 2025 for riociguat, November 7, 2025 for ensitrelvir, and November 11, 2025 for lonafarnib).

2.3 Others

At the initial approval review for the marketing authorization of riociguat, it was determined that co-administration with HIV protease inhibitors should be contraindicated, as with azole antifungal drugs, because of the pharmacokinetic drug interactions. Thereafter, when the contraindications for co-administration of riociguat and HIV protease inhibitors were re-evaluated, the MAH of riociguat submitted the results of clinical studies evaluating the pharmacokinetic drug interactions between riociguat and anti-HIV drugs (Studies 17957 and 18634).

The ratios [90% CI] of the geometric means of AUC of riociguat for co-administration with anti-HIV drugs compared to those of riociguat alone (fed and fasted conditions) were 1.06 (0.62−1.83) for the efavirenz/emtricitabine/tenofovir co-administration group, 2.06 (1.24−3.44) for emtricitabine/rilpivirine/tenofovir co-administration group, 2.06 (1.24−3.44) for elvitegravir/cobicistat/emtricitabine/tenofovir co-administration group, 2.84 (1.70−4.73) for abacavir/dolutegravir/lamivudine co-administration group, and 1.29 (0.77−2.15) for the regimen containing HIV-protease inhibitors group. In these co-administration groups, no particular safety concerns regarding the co-administration of anti-HIV drugs and riociguat were observed.

Of note, using the safety database of the MAH of riociguat, the MAH searched for cases of adverse reactions reported in Japan in which riociguat and anti-HIV drugs[6] were co-administered after September 2022, when the contraindications for co-administration of riociguat and HIV protease inhibitors were changed to precautions for co-administration. As a result, no relevant cases were identified by the search (Date of data lock: September 30, 2025).

In addition, in response to the fact that the contraindication for co-administration of riociguat and itraconazole or voriconazole was changed to precaution for co-administration, there were no adverse reaction cases reported in Japan in which riociguat and itraconazole or voriconazole were co-administered after May 20, 2025 (Date of data lock: September 30, 2025).

3. Statements in Japanese and overseas clinical practice guidelines

Described below are the results of the review of descriptions about the safety of co-administration of riociguat and ensitrelvir or lonafarnib in guidelines for diseases for which

[6] Selected using the Anatomical Therapeutic Chemical (ATC) Classification or WHO Drug Dictionary Codes.

the investigated drugs are indicated.

3.1 Guidelines related to pulmonary hypertension

No specific descriptions were found in the “2025 Guideline on the Management of Pulmonary Thromboembolism, Deep Venous Thrombosis, and Pulmonary Hypertension (the Japanese Circulation Society/Japanese Pulmonary Circulation and Pulmonary Hypertension Society), “Therapy for Pulmonary Arterial Hypertension in Adults Update of the CHEST Guideline and Expert Panel Report (2019) (The American College of Chest Physicians)”, or “2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2022) (European Society of Cardiology [ESC]/ European Respiratory Society [ERS]).”

3.2 Guidelines related to disease caused by SARS-CoV-2 infection

The “2025 Guidelines for the Management of Novel Coronavirus Infections by Five Academic Societies” (2025) (The Japanese Association for Infectious Diseases, The Japanese Respiratory Society, Japanese Society of Chemotherapy, The Japanese Society for Clinical Microbiology, and Japanese Society for Infection Prevention and Control) describes riociguat as a contraindicated concomitant drug, which would lead to increase blood concentrations by competitive inhibition against cytochrome P450 and inhibition against P-gp/BCRP

No specific descriptions were found in the “Novel Coronavirus Infection (COVID-19) Clinical Practice Guidelines Version 10.1 (2024),” “Concept of Drug Treatment for COVID-19 Version 15.1 (2023) (the Japanese Association for Infectious Diseases)”, “COVID-19 rapid guideline: managing COVID-19. (2025) (National Institute for Health and Care Excellence [NICE])”, “Bartoletti M, et al. European society of clinical microbiology and infectious diseases guidelines for coronavirus disease 2019: an update on treatment of patients with mild/moderate disease. Clin Microbiol Infect. 2022;28(12):1578-1590”, “Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. (2024) (National Institutes of Health [NIH])”, “Therapeutics and COVID-19: Living guideline (2025) (World Health Organization)”, or “Clinical management of COVID-19: living guideline (2025) (World Health Organization).”

3.3 Guidelines related to Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies

There were no official guidelines in Japan and overseas.

4. Descriptions in overseas product labeling

Results of the review of the product labeling in the US, the EU, the UK, Canada, and Australia are as follows.

4.1 Riociguat

The current descriptions of overseas product labeling of riociguat are shown in Table 1 in Appendix 2.

Co-administration of riociguat with ensitrelvir or lonafarnib is not contraindicated in the product labeling in any of the counties or regions.

4.2 Ensitrelvir and lonafarnib

The current descriptions of overseas product labeling of ensitrelvir and lonafarnib are shown in Table 2 to 3 in Appendix 2.

For lonafarnib, no descriptions regarding co-administration with riociguat were found. Of note, ensitrelvir is not approved for marketing overseas, and lonafarnib is not approved in Canada or Australia.

IV. PMDA's judgement based on the investigation results

The PMDA considers it acceptable to allow the co-administration of riociguat with ensitrelvir or lonafarnib for the following reasons provided that measures (reducing initial and maintenance doses of riociguat, monitoring signs and symptoms of low blood pressure, etc.) are taken to minimize the risk of hypotension, etc. associated with the increased exposure to riociguat due to the drug interactions:

- For the co-administration of riociguat with ensitrelvir or lonafarnib, no data on pharmacokinetics/safety in clinical trials are available. However, the extent of an increase in exposure to riociguat in co-administration with ensitrelvir or lonafarnib estimated from in vitro studies was similar to or smaller than that observed in co-administration clinical trials of riociguat with clarithromycin or anti-HIV drugs (HIV protease inhibitors, abacavir, etc.), which should be administered with caution when co-administrated. No specific safety concerns were reported in these clinical trials. (See sections II, and Section III-1.1 and 2.3.)

  In addition to the above-mentioned safety information on co-administration with inhibitors of CYP isoforms (clarithromycin, HIV protease inhibitors, abacavir, etc.) that was

obtained at the review for marketing approval of riociguat as well as after marketing approval, taking into account that riociguat is a drug whose administration is to be started from a low dose and whose dose is to be adjusted according to the patient's condition, it is considered that the safety of co-administration of riociguat with ensitrelvir or lonafarnib can be ensured by taking risk minimization measures such as reducing initial and maintenance doses of riociguat and monitoring signs and symptoms of hypotension.

- Co-administration of riociguat with ensitrelvir or lonafarnib is not contraindicated in overseas product labeling[7] (the US, the EU, the UK, Canada, and Australia), and no specific clinical concerns related to co-administration of riociguat with ensitrelvir or lonafarnib were identified in adverse event reports in Japan and overseas, published literature, etc. (See Section III-2.1, 2.2, 3, and 4.)

V. Expert discussion

The PMDA decided that riociguat may be co-administered with ensitrelvir or lonafarnib, provided that risk minimization measures are taken for the hypotension, etc. associated with the increase in exposure to riociguat due to the interactions, and the decision was supported by the expert advisors.

VI. Overall evaluation

The PMDA concluded that PRECAUTIONS may be revised according to Appendix 3, based on the above discussions.

The PMDA considers it appropriate to continue collecting information on the safety of co-administration of riociguat with ensitrelvir or lonafarnib after revising the package inserts and to examine the necessity of additional measures to be taken as needed.

[7] Ensitrelvir is not approved for marketing overseas, and lonafarnib is not approved in Canada or Australia.

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Appendix 1

Summary of investigated drug products

	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
a.	Riociguat	Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg	Bayer Yakuhin Ltd.	INDICATIONS ○ Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or inoperable CTEPH ○ Pulmonary arterial hypertension DOSAGE AND ADMINISTRATION Dose adjustment period The usual initial dosage for adults is 1.0 mg of riociguat administered orally 3 times a day. If systolic blood pressure has remained 95 mmHg or higher for 2 weeks without signs or symptoms of hypotension, the dose should be increased in increments of 0.5 mg at 2-week intervals up to 2.5 mg, administered 3 times a day. If systolic blood pressure is less than 95 mmHg without symptoms of hypotension, the current dose may be maintained. If the patient shows symptoms of hypotension, the dose should be reduced in decrements of 0.5 mg. Dose maintenance period The dose determined during the dose adjustment period should be maintained. Even during the dose maintenance period, the dose should be up to 2.5 mg 3 times a day. If not tolerated (e.g., symptoms of hypotension), the dose should be reduced by 0.5 mg per dose.

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	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
b.	Ensitrelvir fumaric acid	Xocova Tablets 125 mg	Shionogi & Co., Ltd.	INDICATIONS The treatment of disease caused by SARS-CoV-2 infection (COVID-19) DOSAGE AND ADMINISTRATION The usual daily dosage for children aged 12 years or older and adults is 375 mg of ensitrelvir administered orally once a day on the first day, followed by 125 mg administered orally once a day from the second to the fifth day.
c.	Lonafarnib	Zokinvy Capsules 50 mg, 75 mg	AnGes, Inc.	INDICATIONS Hutchinson-Gilford Progeria syndrome and processing-deficient progeroid laminopathies DOSAGE AND ADMINISTRATION The usual starting dosage is 115 mg/m^2 (body surface area) of lonafarnib administered orally twice a day between meals or immediately after a meal, in the morning and the evening, followed by 150 mg/m^2 (body surface area) administered orally 4 months later twice a day between meals or immediately after a meal in the morning and the evening. The dose should be reduced as appropriate according to the patients' condition.

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Appendix 2

Table 1 Related descriptions on concomitant use of riociguat with investigated inhibitors in overseas product labeling

Country/region	Brand name (Version of product labeling)	Description
The US	ADEMPAS (September 2021)	**4 CONTRAINDICATIONS** (No related description) **2 DOSAGE AND ADMINISTRATION** **2.5 Strong CYP and P-gp/BCRP Inhibitors** Consider a starting dose of 0.5 mg, three times a day when initiating Adempas in patients receiving strong cytochrome P450 (CYP) and P-glycoprotein/breast cancer resistance protein (P-gp/BCRP) inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (for example, ritonavir). Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors *[see Warnings and Precautions (5.3), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. **5 WARNINGS AND PRECAUTIONS** **5.3 Hypotension** Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension. **7 DRUG INTERACTIONS** **7.2 Pharmacokinetic Interactions with Adempas** *Strong CYP and P-gp/BCRP inhibitors:* Concomitant use of riociguat with strong cytochrome CYP inhibitors and Pgp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not

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Country/region	Brand name (Version of product labeling)	Description
		tolerate the hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*. **12 CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** Drug interactions: The effect of extrinsic factors on riociguat and M1 were studied in healthy subjects and are shown in Figure 2.

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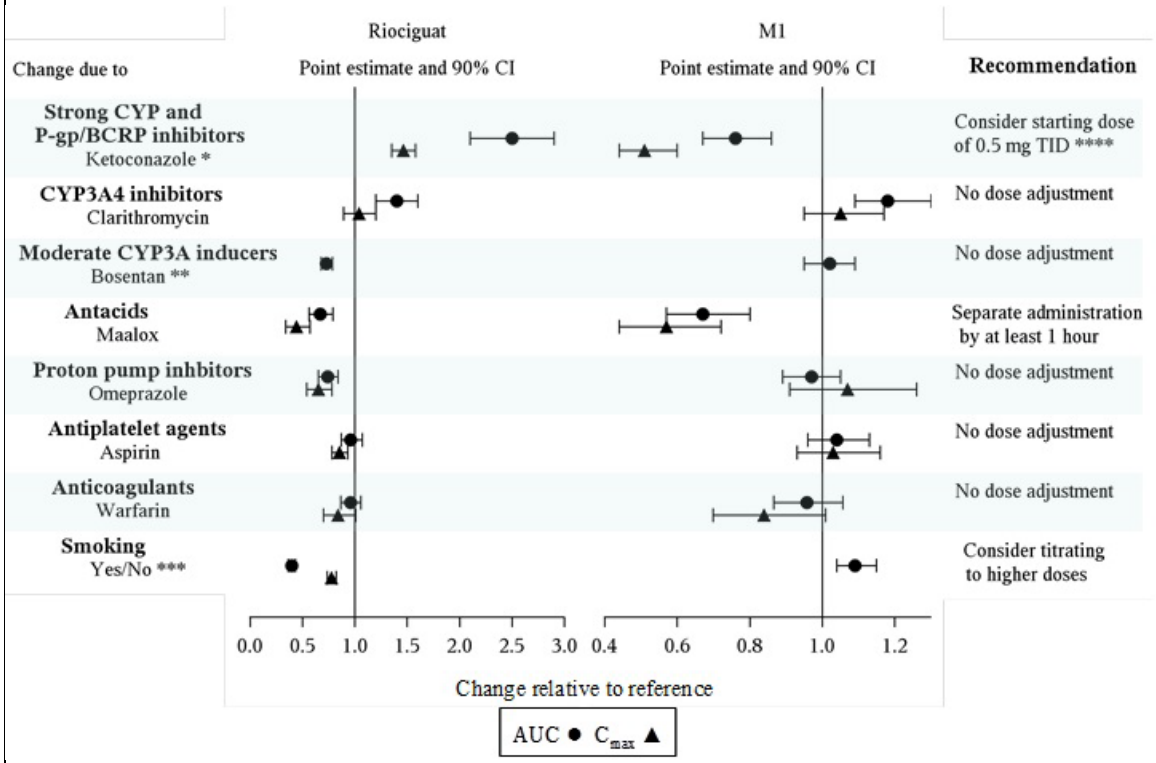
Country/region	Brand name (Version of product labeling)	Description
		Figure 2: Effect of Extrinsic Factors on Riociguat and M1 Pharmacokinetics  **HIV protease inhibitors are strong CYP3A inhibitors and may increase riociguat plasma concentrations to levels similar to those seen with ketoconazole. ** AUC only, estimated using population pharmacokinetics methods *** AUC only for metabolite, estimated using population pharmacokinetics methods. **** Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors [see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.3) and Drug Interactions (7.2)].*

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The EU	ADEMPAS (August 6, 2025)	**4.3 Contraindications** (No related description) **4.2 Posology and method of administration** Special populations *Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors* Coadministration of riociguat with strong multi pathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to riociguat (see section 4.5). When initiating riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg 3 times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on riociguat doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see section 4.5). No clinical data is available in children and adolescents less than 18 years of age receiving concomitant systemic treatment with strong CYP/P-gp and BCRP inhibitors. **4.5 Interaction with other medicinal products and other forms of interaction** Effects of other substances on riociguat *Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors* *The concomitant use of riociguat with strong multi pathway CYP and P-gp/BCRP inhibitors such as azoleantimycotics (e.g. ketoconazole, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) results in a pronounced increase in riociguat exposure. Concomitant administration of HAART combinations led to an increase in riociguat mean AUC of up to about 160% and to an approximate 30% increase in mean Cmax. The safety profile observed in HIV patients taking a single dose of 0.5 mg riociguat together with different combinations of HIV drugs used in HAART was generally comparable to other patient populations. Concomitant administration of 400 mg once daily ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean Cmax. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h.* *Assess the benefit-risk for each patient individually before prescribing riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors.* To mitigate the risk of hypotension when riociguat is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2).

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Country/region	Brand name (Version of product labeling)	Description
		In patients on stable doses of riociguat, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

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The UK	ADEMPAS (October 14, 2025)	**4.3 Contraindications** (No related description) **4.2 Posology and method of administration** *Special populations* *Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors* Coadministration of riociguat with strong multi pathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to riociguat (see section 4.5). When initiating riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg 3 times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on riociguat doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see section 4.5). No clinical data are available in children and adolescents less than 18 years of age receiving concomitant systemic treatment with strong CYP/P-gp and BCRP inhibitors. **4.5 Interaction with other medicinal products and other forms of interaction** Effects of other substances on riociguat Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, CYP3A5, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of unchanged riociguat and renal excretion of unchanged riociguat via glomerular filtration. *Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors* The concomitant use of riociguat with strong multi pathway CYP and P-gp / BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) results in a pronounced increase in riociguat exposure: Concomitant administration of HAART combinations led to an increase in riociguat mean AUC of up to about 160% and to an approximate 30% increase in mean Cmax. The safety profile observed in HIV patients taking a single dose of 0.5 mg riociguat together with different combinations of HIV drugs used in HAART was generally comparable to other patient populations. Concomitant administration of 400 mg once daily ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean Cmax. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h. Assess the benefit-risk for each patient individually before prescribing riociguat in patients on stable doses of strong multi pathway CYP and Pgp/ BCRP inhibitors.

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Country/region	Brand name (Version of product labeling)	Description
		To mitigate the risk of hypotension when riociguat is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2). In patients on stable doses of riociguat, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.
Canada	ADEMPAS (October 13, 2022)	**2 CONTRAINDICATIONS** (No related description) **4.2 Recommended Dose and Dosage Adjustment** **Strong CYP and P-gp/BCRP Inhibitors** Coadministration of ADEMPAS with strong multipathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to ADEMPAS (see 9.2 Drug Interactions Overview). Consider a starting dose of 0.5 mg, three times when initiating ADEMPAS in patients on stable doses of strong multipathway CYP and P-gp/BCRP inhibitors to mitigate risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong multipathway CYP and P-gp/BCRP inhibitors. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors and 9.2 Drug Interactions Overview). **7 WARNINGS AND PRECAUTIONS** **General** Concomitant Use with CYP or P-gp/BCRP Inhibitors The concomitant use of ADEMPAS with strong multi pathway CYP and P-gp/BCRP inhibitors, such as azole antimycotics (eg, ketoconazole, itraconazole), or HIV protease inhibitors (eg, ritonavir) results in a pronounced increase in riociguat exposure (see 9.4 Drug-Drug Interactions), and may result in hypotension. Assess the benefit-risk for each patient individually before prescribing ADEMPAS in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors. Consider a starting dose of 0.5 mg ADEMPAS, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment and consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0

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Country/region	Brand name (Version of product labeling)	Description
		mg if the patient develops signs or symptoms of hypotension (see 4 DOSAGE AND ADMINISTRATION, Strong CYP and P-gp/BCRP Inhibitors and 9.4 Drug-Drug Interactions). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

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9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Antifungal Agents: - Ketoconazoles - Clotrimazole - Itraconazole - Miconazole	CT, I	Concomitant administration of 400 mg once daily ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean C_{max}. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h. Pronounced inhibition of recombinant human CYP1A1 by the antifungal agents was observed *in vitro* (ketoconazole, clotrimazole and miconazole, IC_{50} values of 0.3 to 0.6µm). *In vitro*, riociguat main metabolite M1 formation in human liver microsomes was also inhibited by the antifungal agents (ketoconazole > miconazole > clotrimazole, IC_{50} values of 0.6 to 5.7 µM). Ketoconazole and itraconazole showed inhibitory potency on P-gp/ BCRP mediated efflux of riociguat *in vitro* (ketoconazole $[I_1]/IC_{50}$: 0.01, $[I_2]/IC_{50}$ >10; itraconazole $[I_1]/IC_{50}$: 0.3; $[I_2]/IC_{50}$ >10).	Due to limited clinical experience, ADEMPAS and multi pathway CYP or P-gp/BCRP inhibitors should be co-administered with caution. When initiating ADEMPAS therapy in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. ketoconazole or itraconazole, consider a starting dose of 0.5 mg riociguat, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

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Country/region	Brand name (Version of product labeling)	Description
Australia	ADEMPAS (June 2, 2022)	**4.3 CONTRAINDICATIONS** (No related description) **4.2 DOSE AND METHOD OF ADMINISTRATION** **Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors** Coadministration of ADEMPAS with strong multi pathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to ADEMPAS (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). When initiating ADEMPAS in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see Sections4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** **Concomitant use with other medicinal products** The concomitant use of ADEMPAS with strong multi-pathway CYP and P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) results in a pronounced increase in riociguat exposure (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Pharmacokinetic Interactions). Assess the benefit-risk for each patient individually before prescribing ADEMPAS in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors. Consider a starting dose of 0.5 mg ADEMPAS, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment and consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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Country/region	Brand name (Version of product labeling)	Description
		In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered. **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS** **Pharmacokinetic Interactions** *Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors* Antifungals *In vitro*, ketoconazole, classified as a strong CYP3A4 and P-gp inhibitor, has been shown to be a 'multi-pathway CYP and P-gp/BCRP inhibitor' for riociguat metabolism and excretion. Concomitant administration of ketoconazole 400 mg once daily led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean Cmax. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h. When initiating ADEMPAS therapy in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. ketoconazole or itraconazole, consider a starting dose of 0.5 mg riociguat, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

Table 2 Related descriptions on concomitant use with riociguat in overseas product labeling of ensitrelvir

Country/region	Brand name (Version of product labeling)	Description
The US	(No approval)	
The EU	(No approval)	

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The UK	(No approval)	
Canada	(No approval)	
Australia	(No approval)	

Table 3: Related descriptions on concomitant use with riociguat in overseas product labeling of lonafarnib

Country/region	Brand name (Version of product labeling)	Description
The US	ZOKINVY (July 2025)	(No related description)
The EU	ZOKINVY (October 2023)	(No related description)
The UK	ZOKINVY (September 2024)	(No related description)
Canada	(No approval)	
Australia	(No approval)	

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Appendix 3

(Draft version) Riociguat

Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>10. INTERACTIONS
(Omitted)
10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)
<table>
<tr><th>Drugs</th><th>Signs, symptoms, and treatment</th><th>Mechanism/risk factors</th></tr>
<tr><td>(Omitted)</td><td>(Omitted)</td><td>(Omitted)</td></tr>
<tr><td>Itraconazole, voriconazole
[See Sections 7.1 and 16.7.3.]</td><td>(Omitted)</td><td>(Omitted)</td></tr>
<tr><td>(Omitted)</td><td>(Omitted)</td><td>(Omitted)</td></tr>
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<tr><td>(Omitted)</td><td>(Omitted)</td><td>(Omitted)</td></tr>
<tr><td>Itraconazole, voriconazole
[See Sections 7.1 and 16.7.3.]</td><td>(Omitted)</td><td>(Omitted)</td></tr>
<tr><td><u>Ensitrelvir fumaric acid, lonafarnib</u>
<u>[See Section 7.1]</u></td><td><u>The blood concentration of riociguat may increase.</u>
<u>If administration of riociguat is started</u></td><td><u>The clearance of riociguat is decreased by the inhibition of CYP3A by these drugs.</u></td></tr>
</table></td></tr>
</table>

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		in patients being treated with these drugs, starting at a dose of 0.5 mg 3 times daily should also be considered. If administration of these drugs is started while receiving riociguat, dose reduction of riociguat should be considered.	
	(Omitted)	(Omitted)	(Omitted)

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(Draft version) Ensitrelvir fumaric acid

Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS (This drug is contraindicated in the following patients.) 2.1 (Omitted) 2.2 Patients receiving the following drugs: pimozide, quinidine sulfate hydrate, bepridil hydrochloride hydrate, ticagrelor, eplerenone, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, ergometrine maleate, methylergometrine maleate, dihydroergotamine mesylate, simvastatin, triazolam, anamorelin hydrochloride, ivabradine hydrochloride, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], ibrutinib, blonanserin, lurasidone hydrochloride, azelnidipine, azelnidipine/olmesartan medoxomil, suvorexant, daridorexant hydrochloride, vornorexant hydrate, tadalafil (Adcirca), macitentan/tadalafil, vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, voclosporin, lonafarnib, mavacamten, rivaroxaban, riociguat, apalutamide, carbamazepine, enzalutamide, mitotane,	2. CONTRAINDICATIONS (This drug is contraindicated in the following patients.) 2.1 (Omitted) 2.2 Patients receiving the following drugs: pimozide, quinidine sulfate hydrate, bepridil hydrochloride hydrate, ticagrelor, eplerenone, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, ergometrine maleate, methylergometrine maleate, dihydroergotamine mesylate, simvastatin, triazolam, anamorelin hydrochloride, ivabradine hydrochloride, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], ibrutinib, blonanserin, lurasidone hydrochloride, azelnidipine, azelnidipine/olmesartan medoxomil, suvorexant, daridorexant hydrochloride, ,vornorexant hydrate, tadalafil (Adcirca), macitentan/tadalafil, vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, voclosporin, lonafarnib, mavacamten, rivaroxaban, apalutamide, carbamazepine, enzalutamide, mitotane,

phenytoin, fosphenytoin sodium hydrate, rifampicin, or food containing St. John's Wort [See Section 10.1] 2.3 to 2.4 (Omitted)	phenytoin, fosphenytoin sodium hydrate, rifampicin, or food containing St. John's Wort [See Section 10.1] 2.3 to 2.4 (Omitted)

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10. INTERACTIONS

(Omitted)

10.1 Contraindications for Co-administration (Do not co-administer with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(Omitted)	(Omitted)	(Omitted)
Riociguat [Adempas] [See Section 2.2.]	Ensitrelvir fumaric acid may increase the blood concentration of riociguat. It has been reported that the blood concentration of riociguat was increased and the clearance of riociguat was decreased when	It is considered that the clearance of riociguat is decreased by the inhibitory activity of ensitrelvir fumaric acid against CYP3A and P-glycoprotein/BCRP.

10. INTERACTIONS

(Omitted)

10.1 Contraindications for Co-administration (Do not co-administer with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(Omitted)	(Omitted)	(Omitted)
(Deleted)	(Deleted)	(Deleted)
(Omitted)	(Omitted)	(Omitted)

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	co-administered with ketoconazole.		
(Omitted)	(Omitted)	(Omitted)	

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10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(Omitted)	(Omitted)	The metabolism of these drugs is suppressed by the inhibitory activity of ensitrelvir fumaric acid against CYP3A.
Itraconazole	(Omitted)	
(Omitted)	(Omitted)	(Omitted)

10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(Omitted)	(Omitted)	The metabolism of these drugs is suppressed by the inhibitory activity of ensitrelvir fumaric acid against CYP3A.
Itraconazole	(Omitted)	
Riociguat	Ensitrelvir fumaric acid may increase the blood concentration of riociguat. When co-administration with ensitrelvir fumaric acid is necessary, patients should be monitored for their conditions and dose reduction of	

		riociguat should be considered as necessary.	
(Omitted)	(Omitted)	(Omitted)	

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(Draft version) Lonafarnib

Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS (This drug is contraindicated in the following patients.) 2.1 to 2.2 (Omitted) 2.3 Patients receiving the following drugs: Quinidine sulfate hydrate, bepridil hydrochloride hydrate, ticagrelor, eplerenone, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, methylergometrine maleate, triazolam, anamorelin hydrochloride, ivabradine hydrochloride, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small cell lymphocytic lymphoma)], ibrutinib, blonanserin, lurasidone hydrochloride, azelnidipine containing preparations, suvorexant, tadalafil (Adcirca), vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, rivaroxaban, riociguat, apalutamide, carbamazepine, midazolam, atorvastatin calcium hydrate containing preparations, simvastatin [See Sections 10.1 and 16.7.2] 2.4 (Omitted)	2. CONTRAINDICATIONS (This drug is contraindicated in the following patients.) 2.1 to 2.2 (Omitted) 2.3 Patients receiving the following drugs: Quinidine sulfate hydrate, bepridil hydrochloride hydrate, ticagrelor, eplerenone, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, methylergometrine maleate, triazolam, anamorelin hydrochloride, ivabradine hydrochloride, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small cell lymphocytic lymphoma)], ibrutinib, blonanserin, lurasidone hydrochloride, azelnidipine containing preparations, suvorexant, tadalafil (Adcirca), vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, rivaroxaban, apalutamide, carbamazepine, midazolam, atorvastatin calcium hydrate containing preparations, simvastatin [See Sections 10.1 and 16.7.2] 2.4 (Omitted)

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<table>
<tr>
<td>10. INTERACTIONS
(Omitted)
10.1 Contraindications for Co-administration (Do not co-administer with the following.)
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<tr><th>Drugs</th><th>Signs, symptoms, and treatment</th><th>Mechanism/risk factors</th></tr>
<tr><td>(Omitted)</td><td>(Omitted)</td><td>(Omitted)</td></tr>
<tr><td>Riociguat [Adempas] [See Section 2.3.]</td><td>Lonafarnib may increase the blood concentration of riociguat.</td><td>It is considered that the clearance of riociguat is decreased by the inhibitory activity of lonafarnib against CYP3A and P-glycoprotein.</td></tr>
<tr><td>(Omitted)</td><td>(Omitted)</td><td>(Omitted)</td></tr>
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Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(Omitted)	(Omitted)	(Omitted)
Bosentan hydrate	(Omitted)	(Omitted)
Adrenocorticosteroids	(Omitted)	(Omitted)
(Omitted)		
(Omitted)	(Omitted)	(Omitted)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(Omitted)	(Omitted)	(Omitted)
Bosentan hydrate	(Omitted)	(Omitted)
Riociguat	Lonafarnib may increase the blood concentration of riociguat. When co-administration with lonafarnib is necessary, patients should be monitored for their condition and dose reduction of riociguat should be	The metabolism of these drugs is suppressed by the inhibitory activity of lonafarnib against CYP3A.

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		considered as necessary.	
	Adrenocorticosteroids (Omitted)	(Omitted)	
	(Omitted)		
	(Omitted)	(Omitted)	(Omitted)