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Report on Deliberation

May9, 2025

Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, MHLW

[Non-proprietary name]	a. Riociguat b. Itraconazole c. Voriconazole d. Ensitrelvir fumaric acid e. Lonafarnib
[Brand name]	See Appendix 1 of Report on Investigation Results.
[Marketing authorization holder]	See Appendix 1 of Report on Investigation Results.
[Indications]	See Appendix 1 of Report on Investigation Results.
[Dosage and administration]	See Appendix 1 of Report on Investigation Results.

[Results of deliberation]

It was determined as follows by the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Council held on April 25, 2025:

○ It is acceptable to remove co-administration of riociguat with itraconazole or voriconazole from the Contraindication section and list their concomitant use in the Precautions for Co-administration section, provided that measures are taken to minimize the risk of hypotension, etc. associated with the increased exposure to riociguat due to drug interactions. This decision is based on the comparisons of the increase in exposure to riociguat in co-administration with itraconazole or voriconazole estimated from in vitro studies regarding the drug-drug interaction of these drugs and that observed in the clinical trials in which riociguat was co-administrated with HIV protease inhibitors.

○ On the other hand, the contraindication for co-administration of ensitrelvir fumaric acid and lonafarnib with riociguat should remain unchanged for the following reasons.

- The contraindication for co-administration was established based on the strong CYP3A inhibitory activity of these 2 drugs with reference to other CYP3A inhibitors, at the time these 2 drugs were approved for marketing.
- Since CYP1A1 was found to be the main metabolizing enzyme of riociguat after marketing of riociguat, it was proposed that these 2 drugs be listed in the Precautions for Co-administration section. However, the presence/absence or degree of the inhibitory activity of these 2 drugs against CYP1A1 cannot be

evaluated.

It should be deliberated again after the results of studies, including in vitro studies to confirm the inhibitory activity of these 2 drugs against CYP1A1, are submitted.

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Report on Investigation Results

April 9, 2025

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	a. Riociguat b. Itraconazole c. Voriconazole d. Ensitrelvir fumaric acid e. 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.

Although no results from clinical drug-drug interaction studies had been obtained at the time of the initial approval review of riociguat, co-administration of riociguat and azole antifungal drugs (itraconazole, voriconazole) or human immunodeficiency virus (hereinafter referred to as “HIV”) protease inhibitors (ritonavir, atazanavir, etc.) was contraindicated for the following reasons:

- Riociguat is metabolized mainly by CYP1A1, CYP2C8, CYP2J2, and CYP3A, and it is a substrate of P-glycoprotein (hereinafter referred to as “P-gp”) and breast cancer resistance protein (hereinafter referred to as “BCRP”).
- In a clinical drug-drug interaction study with ketoconazole, which is an inhibitor of multiple CYP isoforms, P-gp, and BCRP (Study 11261), the ratios [90% CI] of the geometric means of C_{max} and AUC after co-administration with ketoconazole to those after administration of riociguat alone were 1.46 [1.35−1.58] and 2.50 [2.14−2.92], respectively, although no particular safety concerns were observed when ketoconazole was concomitantly used.
- Based on the above knowledge, it is considered that a similar increase in exposure to riociguat may occur in co-administration with other azole antifungal drugs or HIV protease inhibitors that inhibit multiple CYP isoforms, P-gp and BCRP, as observed in the co-administration with ketoconazole.

In September 2022, data including the results of clinical trials investigating the pharmacokinetic drug-drug interactions between riociguat and HIV protease inhibitors (Study 17957 and Study 18634) as well as in vitro studies were submitted, and co-administration with HIV protease inhibitors, among the contraindications for co-administration described above, was revised to precaution for co-administration.[1]

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 reasons 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

[1] Report on Investigation Results regarding concomitant use of riociguat and HIV protease inhibitors (https://www.pmda.go.jp/files/000248133.pdf) (in Japanese), (https://www.pmda.go.jp/files/000248159.pdf) (in English)

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.

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 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.

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 itraconazole or voriconazole (Study KINM 240077-ELB) were submitted by the MAH of riociguat. On the other hand, no materials regarding drug-drug interaction between riociguat and ensitrelvir or lonafarnib have been submitted for this investigation. 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]

1.1 In vitro study regarding the drug-drug interaction of riociguat with itraconazole or voriconazole (Study KINM 240077-ELB)

An in vitro study was conducted to evaluate the inhibitory activity of itraconazole or voriconazole against the metabolism of riociguat via CYP1A1 and CYP3A4 and to estimate the effect on the exposure of 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 itraconazole, voriconazole, ketoconazole, or clarithromycin and by measuring the concentrations of M-1, the main metabolite of riociguat, the concentration required for 50% inhibition of CYP1A1 or CYP3A4 by each drug (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 and the estimated fraction metabolized of riociguat for CYP1A1 and CYP3A4[3], the in vivo ratios of AUC of riociguat when co-administered with each drug compared to that for riociguat alone was estimated.[4]

In this study, IC_{50} values against CYP1A1 for itraconazole, voriconazole, ketoconazole, and clarithromycin were 0.12 μmol/L, > 200 μmol/L, 0.034 μmol/L, and > 100 μmol/L, respectively. IC_{50} values against CYP3A4 for itraconazole, voriconazole, ketoconazole, and clarithromycin were 0.061 μmol/L, 0.26 μmol/L, 0.064 μmol/L, and 1.2 μmol/L, respectively.

The AUC ratios of riociguat in co-administration with each active ingredient compared to that of riociguat alone estimated from this study were 1.36 to 3.08 for itraconazole, 1.23 to 1.61 for voriconazole, 1.30 to 3.13 for ketoconazole, and 1.18 to 1.44 for clarithromycin.

The range of AUC ratios of riociguat in co-administration with ketoconazole or clarithromycin estimated from this study were similar to that in co-administration with

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

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

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. Therefore, the MAH of riociguat explained that this study was verified and evaluated as an appropriate in vitro study system to predict the possibility that riociguat would be an object of the drug-drug interaction affected by itraconazole and voriconazole.

The MAH of riociguat explained that itraconazole and voriconazole are expected to impact the riociguat exposure to an extent comparable to that of ketoconazole and clarithromycin, respectively, when riociguat is co-administered with itraconazole or voriconazole 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 itraconazole, voriconazole, ensitrelvir or lonafarnib (hereinafter referred to as “investigated inhibitors” collectively for these 4 drugs) were retrieved from the safety database of the MAH of riociguat, resulting in 12 identified cases (date of data lock: End of July, 2024).

The 12 identified cases included 8 cases for co-administration with itraconazole and 4 cases involving co-administration with voriconazole, among which 1 case for co-administration with itraconazole had been reported in Japan. None of the 12 cases included information on drug interactions, and no cases involving low blood pressure had been reported.

2.2. Published literature

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

[5] Each of the MAHs of the 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, JAPIC-Q, MEDLINE, PubMed, the MAH’s database, etc. (search date: August 20, 2024 for riociguat, August 20, 2024 for itraconazole, July 31, 2024 for voriconazole, August 23, 2024 for ensitrelvir, August 21, 2024 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, similar to 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 (Study 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 for riociguat alone 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: January 21, 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 the investigated inhibitors in guidelines for diseases for which the investigated drugs are indicated.

3.1 Guidelines related to pulmonary hypertension

It is stated that riociguat and azole antifungal drugs (itraconazole, voriconazole) are contraindicated for co-administration in Clinical Practice Guidelines for Chronic

[6] Drugs corresponding to anti-HIV drugs were selected using the Anatomical Therapeutic Chemical Classification (ATC) or the WHO Drug Dictionaries Drug Code.

Thromboembolic Pulmonary Hypertension (CTEPH) 2022 (2022) (Japanese Pulmonary Circulation and Pulmonary Hypertension Society).

No specific descriptions were found in Guidelines for Treatment of Pulmonary Hypertension (2017 edition) (The Japanese Circulation Society, etc.), American College of Chest Physicians Guideline and Expert Panel Report on Pharmacotherapy for PAH (2019) (The American College of Chest Physicians), and 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2022) (European Society of Cardiology).

3.2 Guidelines related to fungal infectious disease

"Riociguat (affected CYP isoform: 3A4), which is indicated for pulmonary hypertension" is listed as one of the drugs contraindicated for co-administration with voriconazole in Clinical Practice Guidelines for TDM of Antimicrobial Drugs 2022 (2022) (Japan Society of Chemotherapy/The Japanese Society of Therapeutic Drug Monitoring).

No specific descriptions were found in the following guidelines: Guidelines for the Diagnosis and Treatment of Deep-Seated Mycosis 2014 (2014) (the committee for preparation of guidelines for deep-seated mycosis), Guidelines for Diagnosis and Treatment of Aspergillosis 2015 (2015) (The Japanese Society for Medical Mycology), Clinical Practice Guidelines for Cutaneous Fungal Disease 2019 by the Japanese Dermatological Association (2019) (The Japanese Dermatological Association), Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis 2019 (2019) (The Japanese Society for Medical Mycology), Guidelines for Hematopoietic Cell Transplantation; Prevention and Treatment of Fungal Infectious Disease (2nd Edition) (2021) (Japanese Society for Transplantation and Cellular Therapy), Clinical Practice Guidelines for Management of Invasive Candidiasis (2021) (The Japanese Society for Medical Mycology), Guidelines for the Diagnosis and Treatment of Rare Deep Mycoses (2024) (The Japanese Society for Medical Mycology), Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America (2015) (Infectious Diseases Society of America (IDSA)), Clinical Practice Guideline for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America (2016) (Infectious Diseases Society of America (IDSA)), Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management (2016), Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMIDECMM-ERS guideline (2017), and ECMM/ISHAM/ASM Global

Guideline for the Diagnosis and Management of Cryptococcosis (2024).

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

No specific descriptions were found in the following guidelines: Concept of Drug Treatment for COVID-19 Version 15.1 (2023) (The Japanese Association for Infectious Diseases), Novel Coronavirus Infection (COVID-19) Clinical Practice Guidelines Version 10.1 (2024), 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, Therapeutics and COVID-19: Living guideline (2023) (World Health Organization), COVID-19 rapid guideline: managing COVID-19 (2024) (National Institute for Health and Care Excellence (NICE)), Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (2024) (National Institutes of Health(NIH)).

3.4 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

The 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 itraconazole, voriconazole, ensitrelvir, or lonafarnib is not contraindicated in the product labeling in any of the countries or regions, and it is described as follows: It should be considered that administration of riociguat be started with an initial dose of 0.5 mg 3 times a day in patients treated with azole antifungal drugs (ketoconazole, itraconazole, etc.), which are strong CYP and P-gp/BCRP inhibitors; signs and symptoms of low blood pressure should be monitored.

4.2 Itraconazole, voriconazole, ensitrelvir, and lonafarnib

The current descriptions of overseas product labeling of the investigated inhibitors are shown in Table 2 to Table 5 in Appendix 2.

For itraconazole, co-administration with riociguat is not contraindicated in the product labeling in any of the countries or regions. However, it is described as follows: Co-administration is not recommended; the use of riociguat is not recommended during and for 2 weeks after treatment with itraconazole.

For voriconazole and 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 itraconazole, voriconazole, 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 co-administration of riociguat with itraconazole or voriconazole, no data on pharmacokinetics/safety in clinical trials are available. However, the extent of the increase in exposure to riociguat in co-administration with itraconazole or voriconazole estimated from in vitro studies was similar to that observed in co-administration of riociguat with ketoconazole or anti-HIV drugs (HIV protease inhibitors, abacavir, etc.) in clinical trials. No specific safety concerns were reported in these clinical trials. (See sections II, 1.1 and 2.3 of III.)

  In addition to the above-mentioned safety information on co-administration with inhibitors of CYP isoforms (ketoconazole, 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 itraconazole or voriconazole can be ensured by taking risk minimization measures such as reducing

initial and maintenance doses of riociguat and monitoring signs and symptoms of low blood pressure.

- For the co-administration of riociguat with ensitrelvir or lonafarnib, no data on pharmacokinetics/safety in clinical trials are available. However, based on the following fact, it was considered not rational to maintain the contraindications for co-administration of riociguat with ensitrelvir or lonafarnib in cases where the contraindication for co-administration of riociguat with itraconazole or voriconazole, which is a strong CYP3A inhibitor, is lifted: It was shown that riociguat is metabolized mainly by CYP1A1, while co-administration with ensitrelvir or lonafarnib was contraindicated with reference to other strong CYP3A inhibitors when ensitrelvir and lonafarnib were approved for marketing.
- Co-administration of riociguat with itraconazole, voriconazole, ensitrelvir, or lonafarnib is not contraindicated in overseas product labeling[7] (the US, the EU, the UK, Canada, Australia), and no specific clinical concerns related to co-administration of riociguat with itraconazole, voriconazole, ensitrelvir, or lonafarnib were identified in adverse event reports in Japan and overseas, published literature, etc. (See sections 2.1, 2.2, 3, and 4 of III.)

V. Expert discussion

The PMDA decided that riociguat may be co-administered with itraconazole, voriconazole, 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 all 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 itraconazole, voriconazole, 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 the systolic blood pressure remains greater than 95 mmHg for 2 weeks and the patient shows no signs or symptoms of hypotension, the dose should be increased by 0.5 mg at 2-week intervals up to the maximum daily dose of 2.5 mg 3 times a day. If the systolic blood pressure is less than 95 mmHg but the patient shows no signs or symptoms of hypotension, the current dose should be maintained. If the patient shows signs or symptoms of hypotension, the dose should be reduced by 0.5 mg per dose. Dose maintenance period The dose determined during the dose adjustment period should be maintained. The maximum daily dose is 2.5 mg 3 times a day during the dose maintenance period as well. If not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced by 0.5 mg per dose.
b.	Itraconazole	Itrizole Capsules 50, Itrizole Oral Solution 1%, and the others	Janssen Pharmaceutical K.K. and the others	<Itrizole Capsules 50> INDICATIONS <Applicable microorganisms> Dermatophytes (genus *Trichophyton*, genus *Microsporum*, genus *Epidermophyton*),

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	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				genus *Candida*, genus *Malassezia*, genus *Aspergillus*, genus *Cryptococcus*, genus *Sporothrix*, genus *Fonsecaea* <Applicable conditions> •Visceral mycosis (deep mycosis) Fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis •Deep cutaneous mycosis Sporotrichosis, chromomycosis •Superficial cutaneous mycosis (excluding nail tinea) Tinea: Body tinea, tinea cruris, tinea manuum, tinea pedis, tinea capitis, kerion celsi, tinea barbae Candidiasis: Oral candidiasis, cutaneous candidiasis, nail candidiasis, candidal paronychia and onychia, candida sycosis, chronic mucocutaneous candidiasis, tinea versicolour, malassezia folliculitis •Nail tinea DOSAGE AND ADMINISTRATION <Visceral mycosis (deep mycosis)> The usual adult dosage is 100 to 200 mg of itraconazole administered orally once a day immediately after a meal. The dose should be adjusted depending on the age or symptoms of the patients. However, if this drug is switched from itraconazole injection, the usual daily dosage is 200 mg twice a day (400 mg daily) administered orally immediately after a meal. <Deep cutaneous mycosis> The usual adult dosage is 100 to 200 mg of itraconazole administered orally once a day immediately after a meal. The dose should be adjusted depending on the age or symptoms of the patients. However, the maximum daily dose should be 200 mg.

	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				<Superficial cutaneous mycosis (excluding nail tinea> The usual daily dosage for adults is 50 to 100 mg of itraconazole administered orally once a day immediately after a meal. However, for nail candidiasis and candidal paronychia and onychia, 100 mg of itraconazole should be administered orally once a day immediately after a meal. The dose should be adjusted depending on the age or symptoms of the patients. However, the maximum daily dose should be 200 mg. <Nail tinea (pulse therapy)> The usual adult dosage is 200 mg of itraconazole twice a day (400 mg daily) administered orally immediately after a meal for one week, followed by temporary discontinuation for 3 weeks. This is defined as one cycle, and 3 cycles are repeated. The dose should be reduced as necessary. <Itrizole Oral Solution 1%> INDICATIONS •Fungal infection <Applicable microorganisms> Genus *Aspergillus*, genus *Candida*, genus *Cryptococcus*, genus *Blastomyces*, genus *Histoplasma* <Applicable conditions> Fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, oropharyngeal candidiasis, oesophageal candidiasis, blastomycosis, histoplasmosis •Prophylaxis of deep mycosis in patients with haematological malignancy or haematopoietic stem cell transplant patients who are expected to have neutropenia DOSAGE AND ADMINISTRATION <Fungal infection>

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	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				•Fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis The usual daily dosage for adults is 20 mL (200 mg as itraconazole) administered orally once a day in the fasted state. The dose should be adjusted depending on the age or symptoms of the patients. However, the maximum single dose is 20 mL and the maximum daily dose is 40 mL. •Oropharyngeal candidiasis, oesophageal candidiasis The usual daily dosage for adults is 20 mL (200 mg as itraconazole) administered orally once a day in the fasted state. <Prophylaxis of deep mycosis in patients with haematological malignancy or haematopoietic stem cell transplant patients who are expected to have neutropenia> The usual daily dosage for adults is 20 mL (200 mg as itraconazole) administered orally once a day in the fasted state. The dose should be adjusted depending on the symptoms of the patients. However, the maximum single dose is 20 mL and the maximum daily dose is 40 mL.

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<table>
<tr><th></th><th>Non-proprietary name</th><th>Brand name</th><th>Marketing authorization holder</th><th>Indications/dosage and administration</th></tr>
<tr><td>c.</td><td>Voriconazole</td><td>Vfend Tablets 50 mg, 200 mg, Vfend for Intravenous Use 200 mg, Vfend Dry Syrup 2800 mg, and the others</td><td>Pfizer Japan Inc. and the others</td><td>INDICATIONS
<Vfend Tablets 50 mg, 200 mg, Vfend Dry Syrup 2800 mg>
•The following severe or refractory fungal infections
·Invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis
·Candidaemia, oesophageal candidiasis, candida peritonitis, bronchial/pulmonary candidiasis
·Cryptococcal meningitis, pulmonary cryptococcosis
·Fusariosis
·Scedosporiosis
•Prophylaxis of deep mycosis in haematopoietic stem cell transplant patients
<Vfend for Intravenous Use 200 mg>
•The following severe or refractory fungal infections
·Invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis
·Candidaemia, candida peritonitis, bronchial/pulmonary candidiasis
·Cryptococcal meningitis, pulmonary cryptococcosis
·Fusariosis
·Scedosporiosis
•Prophylaxis of deep mycosis in haematopoietic stem cell transplant patients

DOSAGE AND ADMINISTRATION
<Vfend Tablets 50 mg, 200 mg, Vfend Dry Syrup 2800 mg>
<table><tr><td>Adults (body weight equal to or greater than 40 kg)</td><td>The usual daily dosage is 300 mg of voriconazole administered orally between meals twice a day on the first day of administration, followed by 150 mg/dose or 200</td></tr></table></td></tr>
</table>

	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				mg/dose administered orally between meals twice a day on the second day and thereafter. The dose may be increased depending on the patients' condition or if the patients do not sufficiently respond to the drug. The maximum dosage on the first day is 400 mg per dose administered twice a day, and the maximum dosage on the second day and thereafter is 300 mg per dose administered twice a day.
				Adult (body weight less than 40 kg): The usual daily dosage is 150 mg of voriconazole administered orally between meals twice a day on the first day of administration, followed by 100 mg per dose administered orally between meals twice a day on the second day and thereafter. The dose on the second day and thereafter may be increased up to 150 mg twice a day depending on the patients' condition or if the patients do not sufficiently respond to the drug.
				Children (aged 2 years or older and younger than 12 years or those aged 12 years or older and who weigh less than 50 kg): The usual dosage is 9 mg/kg of voriconazole administered orally between meals twice a day following administration of voriconazole injection. The dose may be increased by 1 mg/kg depending on the patients' condition or if the patients do not sufficiently respond to the drug. If it is not tolerated, the dose may be decreased by 1 mg/kg. (If 350 mg is used as the

<table>
<tr><th></th><th>Non-proprietary name</th><th>Brand name</th><th>Marketing authorization holder</th><th>Indications/dosage and administration</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>maximum dose, the dose may be decreased by 50 mg.)
However, the maximum dosage is 350 mg per dose administered twice a day.</td></tr>
<tr><td>Children (aged 12 years or older and who weigh 50 kg or more)</td><td>The usual dosage is 200 mg of voriconazole administered orally between meals twice a day following administration of voriconazole injection. The dose may be increased up to 300 mg/dose twice a day depending on the patients' condition or if the patients do not sufficiently respond to the drug.</td></tr>
</table>
<Vfend for Intravenous Use 200 mg>
<table>
<tr><td>Adults</td><td>The usual daily dosage is 6 mg/kg of voriconazole administered by intravenous infusion twice a day on the first day, followed by administration of 3 mg/kg or 4 mg/kg per dose of intravenous infusion twice a day on the second day and thereafter.</td></tr>
<tr><td>Children (aged 2 years or older and younger than 12 years or those aged 12 years or older and who weigh less than 50 kg)</td><td>The usual daily dosage is 9 mg/kg of voriconazole administered by intravenous infusion twice a day on the first day, followed by administration of 8 mg/kg per dose of intravenous infusion twice a day on the second day and thereafter.
The dose may be increased by 1 mg/kg depending on the patients' condition or if the</td></tr>
</table>
</td></tr>
</table>

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<table>
<tr><th></th><th>Non-proprietary name</th><th>Brand name</th><th>Marketing authorization holder</th><th>Indications/dosage and administration</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>patients do not sufficiently respond to the drug. If it is not tolerated, the dose may be decreased by 1 mg/kg.</td></tr>
<tr><td>Children (aged 12 years or older and who weigh 50 kg or more)</td><td>The usual daily dosage is 6 mg/kg of voriconazole administered by intravenous infusion twice a day on the first day, followed by administration of 4 mg/kg per dose of intravenous infusion twice a day on the second day and thereafter.</td></tr>
</table>
</td></tr>
<tr><td>d.</td><td>Ensitrelvir fumaric acid</td><td>Xocova Tablets 125 mg</td><td>Shionogi & Co., Ltd.</td><td>INDICATIONS
The treatment of disease caused by SARS-CoV-2 infection (COVID-19)</td></tr>
</table>

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	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				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.
e.	Lonafarnib	Zokinvy capsules 50 mg, 75 mg	AnGes, Inc.	INDICATIONS The treatment of 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 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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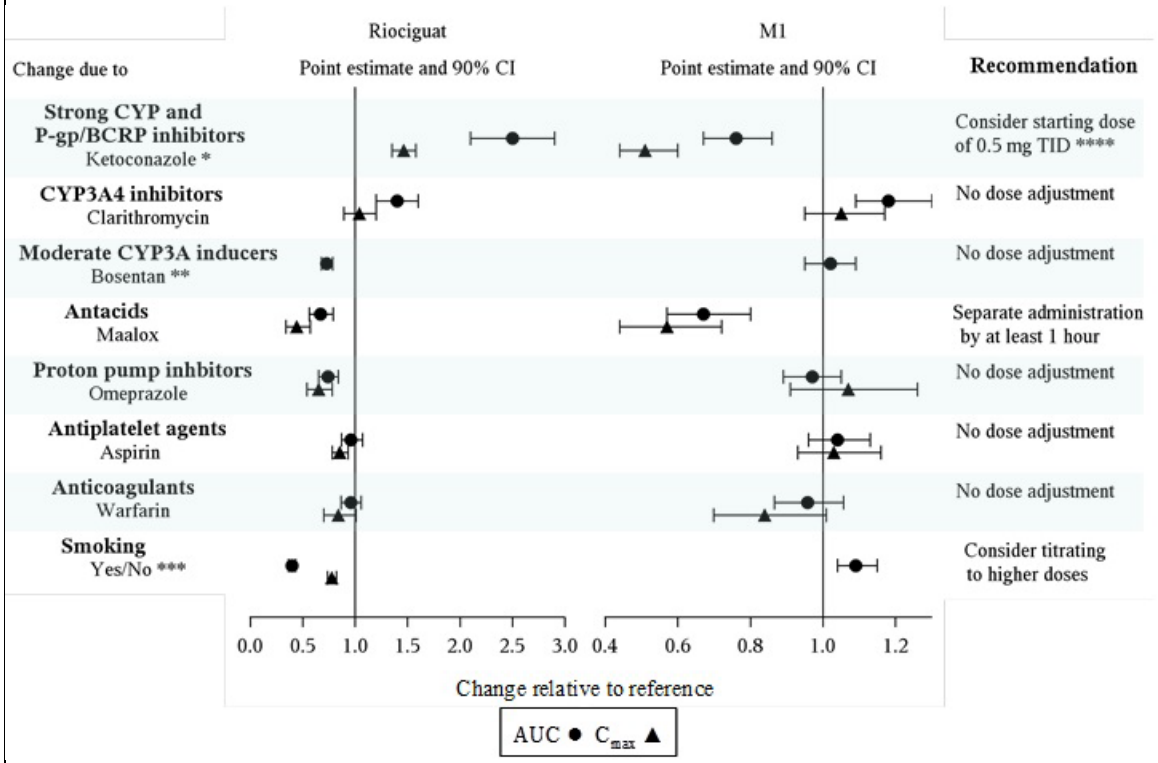
Figure 2: Effect of Extrinsic Factors on Riociguat and M1 Pharmacokinetics



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),*

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		Warnings and Precautions (5.3) and Drug Interactions (7.2)].
The EU	ADEMPAS (August 1, 2024)	**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 sections 4.4 and 4.5). No clinical data is available in children receiving concomitant systemic treatment with strong CYP/P-gp and BCRP inhibitors. **4.4 Special warnings and precautions for use** Concomitant use with other medicinal products • 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 (see sections 4.5 and 5.2). • 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, consider dose reduction and monitoring for signs and symptoms of hypotension (see sections 4.2 and 4.5). • 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. • The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong

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		P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see sections 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered. **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* *Highly active antiretroviral therapy (HAART)* 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, e.g. as contained in HAART, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4). *Antifungals* *In vitro*, ketoconazole, classified as a strong CYP3A4 and P-glycoprotein (P-gp) inhibitor, has been shown to be a multi-pathway CYP and P-gp/breast cancer resistance protein (BCRP) inhibitor for riociguat metabolism and excretion (see section 5.2). 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. 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, e.g. ketoconazole, posaconazole or itraconazole consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4).
The UK	ADEMPAS (October 5, 2023)	**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 sections 4.4 and 4.5). No clinical data is available in children receiving concomitant systemic treatment with strong CYP/P-gp and BCRP inhibitors. **4.4 Special warnings and precautions for use** **Concomitant use with other medicinal products** • 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 (see sections 4.5 and 5.2). • 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, consider dose reduction and monitoring for signs and symptoms of hypotension (see sections 4.2 and 4.5). • 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. • The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see sections 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered. **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*

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		Highly active antiretroviral therapy (HAART) 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, e.g. as contained in HAART, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4). *Antifungals* *In vitro*, ketoconazole, classified as a strong CYP3A4 and P-glycoprotein (P-gp) inhibitor, has been shown to be a multi-pathway CYP and P-gp/breast cancer resistance protein (BCRP) inhibitor for riociguat metabolism and excretion (see section 5.2). 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. 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, e.g. ketoconazole, posaconazole or itraconazole consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4).
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).

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		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 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. **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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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). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not

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		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 itraconazole

Country/region	Brand name (Version of product labeling)	Description
The US	SPORANOX (March, 2024)	**CONTRAINDICATIONS** (No related description) **Drug Interactions**

		Prevention or Management: Not recommended during and 2 weeks after SPORANOX® treatment.
The EU	SPORANOX (June 24, 2024)	**4.3 Contraindications** (No related description) **4.5 Interaction with other medicinal products and other forms of interaction** Expected/Potential effect on drugs levels: Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. Clinical comment: Not recommended
The UK	SPORANOX (July 22, 2024)	**4.3 Contraindications** (No related description) **4.5 Interaction with other medicinal products and other forms of interaction** Expected/Potential effect on drugs levels: Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. Clinical comment: Not recommended
Canada	SPORANOX (October 3, 2023)	**2 CONTRAINDICATIONS** (No related description) **9.4 Drug-Drug Interactions** Clinical comment: NOT RECOMMENDED during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the cardiovascular drug.
Australia	SPORANOX (July 17, 2024)	**4.3 CONTRAINDICATIONS** (No related description) **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS** Clinical comment: Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the cardiovascular drug.

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

Country/region	Brand name (Version of product labeling)	Description
The US	VFEND (August, 2024)	(No related description)
The EU	VFEND (April 4, 2024)	(No related description)
The UK	VFEND (November 12, 2024)	(No related description)
Canada	VFEND (May 8, 2024)	(No related description)
Australia	VFEND (October 2, 2024)	(No related description)

Table 4　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)	
The UK	(No approval)	
Canada	(No approval)	
Australia	(No approval)	

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Table 5　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 (March 21, 2024)	(No related description)
The EU	ZOKINVY (January 6, 2025)	(No related description)
The UK	ZOKINVY (August, 2022)	(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>2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 to 2.6 (omitted)
2.7 Patients receiving azole antifungal drugs (itraconazole, voriconazole)
2.8 (omitted)

10. INTERACTIONS
Riociguat is mainly metabolized by CYP1A1, CYP2C8, CYP2J2, and CYP3A. Riociguat is a substrate of P-glycoprotein/breast cancer resistance protein (P-gp/BCRP). Therefore, the plasma concentration of riociguat may be affected by the inhibitors or inducers of CYP and P-gp/BCRP. In addition, riociguat and its main metabolite M-1 are CYP1A1 inhibitors (in vitro).

10.1 Contraindications for Co-administration (Do not co-administer 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></table></td><td>2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 to 2.6 (omitted)
(deleted)

2.7 (omitted)

10. INTERACTIONS
Riociguat is mainly metabolized by CYP1A1, and is partly metabolized by CYP3A. Riociguat is a substrate of P-glycoprotein/breast cancer resistance protein (P-gp/BCRP). In addition, riociguat and its main metabolite M-1 are CYP1A1 inhibitors.

10.1 Contraindications for Co-administration (Do not co-administer 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></table></td></tr>
</table>

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Azole antifungal drugs Itraconazole (Itrizole) Voriconazole (Vfend)	When co-administered with ketoconazole (oral dosage form, not marketed in Japan), the AUC and C_{max} of riociguat were increased by 150% and 46%, respectively. In addition, the elimination half-life was prolonged, and the clearance was also decreased.	The clearance of riociguat is decreased by the inhibition of multiple CYP isoforms (CYP1A1, CYP3A, etc.) and P-gp/BCRP.	(deleted)	(deleted)	(deleted)
(omitted)	(omitted)	(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)	(omitted)
Preparations containing ritonavir Atazanavir Preparations containing rilpivirine Preparations containing cobicistat Preparations containing abacavir Preparations containing darunavir	The blood concentration of riociguat may increase. If administration of riociguat is started in patients being treated with these drugs, starting at a dose of 0.5 mg 3 times a day should	The clearance of riociguat is decreased by the inhibition of CYP1A1 and/or CYP3A by these drugs.

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)	(omitted)
Preparations containing ritonavir Atazanavir Preparations containing rilpivirine Preparations containing cobicistat Preparations containing abacavir Preparations containing darunavir	The blood concentration of riociguat may increase. If administration of riociguat is started in patients being treated with these drugs, starting at a dose of 0.5 mg 3 times a day should	The clearance of riociguat is decreased by the inhibition of CYP1A1 and/or CYP3A by these drugs.

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Fosamprenavir	also be considered.	
(omitted)	(omitted)	(omitted)

Fosamprenavir	also be considered. If administration of these drugs is started while receiving riociguat, dose reduction of riociguat should be considered.	
Itraconazole, voriconazole	The blood concentration of riociguat may increase. If administration of riociguat is started in patients being treated with these drugs, starting at a dose of 0.5 mg 3 times a day should also be considered. If administration of these drugs is started while receiving riociguat, dose reduction of riociguat should be considered.	The clearance of riociguat is decreased by the inhibition of CYP1A1 and/or CYP3A by these drugs.

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Ensitrelvir fumaric acid, lonafarnib	The blood concentration of riociguat may increase. If administration of riociguat is started in patients being treated with these drugs, starting at a dose of 0.5 mg 3 times a day should also be considered. If administration of these drugs is started while receiving riociguat, dose reduction of riociguat should be considered.	The clearance of riociguat is decreased by the strong inhibition of CYP3A .
(omitted)	(omitted)	(omitted)

16. PHARMACOKINETICS

16.1 to16.3 (omitted)

16.4 Metabolism

Riociguat is demethylated mainly by CYP1A1, CYP2C8, CYP2J2, and CYP3A, and its main metabolite M-1 is formed (in vitro). Thereafter, it is metabolized to N-glucuronide conjugates that lack pharmacological activity. It has been reported that CYP1A1, which is involved in the formation of the main metabolites in the liver and lungs, is mediated by polycyclic aromatic hydrocarbons that are

16. PHARMACOKINETICS

16.1 to 16.3 (omitted)

16.4 Metabolism

Riociguat is demethylated mainly by CYP1A1, CYP2J2, and CYP3A, and its main metabolite, M-1, is formed (in vitro). Thereafter, it is metabolized to N-glucuronide conjugates that lack pharmacological activity. It has been reported that CYP1A1, which is involved in the formation of the main metabolites in the liver and lungs, is mediated by polycyclic aromatic hydrocarbons that are contained in cigarette

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contained in cigarette smoke, etc.	smoke, etc.
16.6 (omitted)	16.6 (omitted)
16.7. Drug-Drug Interaction	16.7. Drug-Drug Interaction
16.7.1 to 16.7.2 (omitted)	16.7.1 to 16.7.2 (omitted)
16.7.3 Ketoconazole (oral dosage form: Not marketed in Japan) A single dose of riociguat 0.5 mg alone or a single concomitant dose of riociguat following administration of ketoconazole 400 mg once a day for 4 days was administered after a meal in a crossover study in 16 healthy adult subjects. The C_{max} and AUC of riociguat were increased by 46% and approximately 150%, respectively, by co-administration with ketoconazole. The C_{max} and AUC of the metabolite M-1 were decreased by 49% and 24%, respectively[13]. (non-Japanese data).	16.7.3 Ketoconazole (oral dosage form: Not marketed in Japan) A single dose of riociguat 0.5 mg alone or a single concomitant dose of riociguat following administration of ketoconazole 400 mg once a day for 4 days was administered after a meal in a crossover study in 16 healthy adult subjects. The C_{max} and AUC of riociguat were increased by 46% and approximately 150%, respectively, by co-administration with ketoconazole. The C_{max} and AUC of the metabolite M-1 were decreased by 49% and 24%, respectively[13]. (non-Japanese data).
16.7.4 to 16.7.8 (omitted)	16.7.4 to 16.7.8 (omitted)

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(Draft version) Itraconazole

Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 Patients receiving the following drugs: Pimozide, quinidine, bepridil, triazolam, simvastatin, azelnidipine, azelnidipine/olmesartan medoxomil, nisoldipine, ergotamine/caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine, vardenafil, eplerenone, blonanserin, sildenafil (Revatio), tadalafil (Adcirca), suvorexant, ibrutinib, ticagrelor, lomitapide, ivabradine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], lurasidone hydrochloride, anamorelin hydrochloride, finerenone, isavuconazonium sulfate, aliskiren, dabigatran, rivaroxaban, riociguat
2.2 to 2.5 (omitted)

10. INTERACTIONS
(omitted)
10.1 Contraindications for Co-administration (Do not co-administer 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></table></td><td>2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 Patients receiving the following drugs: Pimozide, quinidine, bepridil, triazolam, simvastatin, azelnidipine, azelnidipine/olmesartan medoxomil, nisoldipine, ergotamine/caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine, vardenafil, eplerenone, blonanserin, sildenafil (Revatio), tadalafil (Adcirca), suvorexant, ibrutinib, ticagrelor, lomitapide, ivabradine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], lurasidone hydrochloride, anamorelin hydrochloride, finerenone, isavuconazonium sulfate, aliskiren, dabigatran, rivaroxaban
2.2 to 2.5 (omitted)

10. INTERACTIONS
(omitted)
10.1 Contraindications for Co-administration (Do not co-administer 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></table></td></tr>
</table>

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Riociguat (Adempas)	Itraconazole may increase the blood concentration of riociguat. (It has been reported as follows: When co-administered with ketoconazole, the AUC and C_{max} of riociguat were increased by 150% and 46%, respectively; in addition, the elimination half-life was prolonged, and the clearance was also decreased.)	It is considered that the clearance of riociguat is decreased by the inhibitory activity of itraconazole against CYP3A4 and P-glycoprotein.

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)	(omitted)

(deleted)	(deleted)	(deleted)

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)	(omitted)
Riociguat	Itraconazole may increase the blood concentration of riociguat. (It has been reported as follows: When co-administered with ketoconazole, the AUC and C_{max} of	It is considered that the clearance of riociguat is decreased by the inhibitory activity of itraconazole against CYP1A1 and CYP3A4.

		riociguat were increased by 150% and 46%, respectively; in addition, the elimination half-life was prolonged.) When co-administration with itraconazole is necessary, patients should be monitored for their conditions and dose reduction of riociguat should be considered as necessary.	

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(Draft version) Voriconazole

Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 Patients receiving the following drugs: Rifampicin, rifabutin, efavirenz, ritonavir, lopinavir/ritonavir, nirmatrelvir/ritonavir, carbamazepine, barbital, phenobarbital, pimozide, quinidine, ivabradine, ergot alkaloids (ergotamine/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine), triazolam, ticagrelor, asunaprevir, lomitapide, blonanserin, suvorexant, rivaroxaban, riociguat, azelnidipine, olmesartan medoxomil/azelnidipine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], anamorelin, lurasidone, isavuconazonium, finerenone
2.2 to 2.3 (omitted)

10. INTERACTIONS
(omitted)
10.1 Contraindications for Co-administration (Do not co-administer with the following.)
<table>
<tr><th>Drugs</th><th>Signs, symptoms, and treatment</th><th>Mechanism/risk factors</th></tr>
</table>
</td><td>2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 Patients receiving the following drugs: Rifampicin, rifabutin, efavirenz, ritonavir, lopinavir/ritonavir, nirmatrelvir/ritonavir, carbamazepine, barbital, phenobarbital, pimozide, quinidine, ivabradine, ergot alkaloids (ergotamine/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine), triazolam, ticagrelor, asunaprevir, lomitapide, blonanserin, suvorexant, rivaroxaban, azelnidipine, olmesartan medoxomil/azelnidipine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], anamorelin, lurasidone, isavuconazonium, finerenone
2.2 to 2.3 (omitted)

10. INTERACTIONS
(omitted)
10.1 Contraindications for Co-administration (Do not co-administer with the following.)
<table>
<tr><th>Drugs</th><th>Signs, symptoms, and treatment</th><th>Mechanism/risk factors</th></tr>
</table>
</td></tr>
</table>

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(omitted)	(omitted)	(omitted)
Riociguat (Adempas)	The blood concentration of riociguat may be increased by co-administration with voriconazole.	Voriconazole inhibits multiple CYP isoforms (CYP1A1, CYP3A, etc.), which are the metabolizing enzyme of riociguat.
(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)	(omitted)

(omitted)	(omitted)	(omitted)
(deleted)	(deleted)	(deleted)
(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)	(omitted)
Riociguat	The blood concentration of riociguat may be increased by co-administration with voriconazole. When co-administration with voriconazole is necessary, patients should be monitored for their conditions and dose reduction of riociguat should be considered as necessary.	Voriconazole inhibits the metabolizing enzyme of riociguat (CYP3A).

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(Draft version) Ensitrelvir fumaric acid

Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS (This drug is contraindicated to 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, tadalafil (Adcirca), macitentan/tadalafil, vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, voclosporin, lonafarnib, rivaroxaban, riociguat, apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, fosphenytoin sodium hydrate, rifampicin, or food containing St. John's Wort 2.3 to 2.4 (omitted)	2. CONTRAINDICATIONS (This drug is contraindicated to 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, tadalafil (Adcirca), macitentan/tadalafil, vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, voclosporin, lonafarnib, rivaroxaban, apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, fosphenytoin sodium hydrate, rifampicin, or food containing St. John's Wort 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)	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 co-administered with ketoconazole.	It is considered that the clearance of riociguat is decreased by the inhibitory activity of ensitrelvir fumaric acid against CYP3A and P-glycoprotein/BCRP.
(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)	(omitted)

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)

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
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.	suppressed by the inhibitory activity of ensitrelvir fumaric acid against CYP3A.

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(Draft version) Lonafarnib

Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 to 2.2 (omitted)	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 lymphocytic lymphoma)], ibrutinib, blonanserin, lurasidone hydrochloride, preparations containing azelnidipine, suvorexant, tadalafil (Adcirca), vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, rivaroxaban, riociguat, apalutamide, carbamazepine, midazolam, preparations containing atorvastatin calcium hydrate, simvastatin	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 lymphocytic lymphoma)], ibrutinib, blonanserin, lurasidone hydrochloride, preparations containing azelnidipine, suvorexant, tadalafil (Adcirca), vardenafil hydrochloride hydrate, lomitapide mesilate, rifabutin, finerenone, rivaroxaban, apalutamide, carbamazepine, midazolam, preparations containing atorvastatin calcium hydrate, simvastatin
2.4 (omitted)	2.4 (omitted)
10. INTERACTIONS	10. INTERACTIONS
(omitted)	(omitted)
10.1 Contraindications for Co-administration (Do not co-administer with	10.1 Contraindications for Co-administration (Do not co-administer with

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the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(omitted)	(omitted)	(omitted)
Riociguat [Adempas]	Lonafarnib may increase the blood concentration of riociguat.	It is considered that the clearance of riociguat is decreased by the inhibitory activity of lonafarnib against CYP3A and P-glycoprotein.
(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)	(omitted)
Bosentan hydrate	(omitted)	(omitted)
Adrenocorticosteroids	(omitted)	(omitted)
(omitted)	(omitted)	(omitted)

the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
(omitted)	(omitted)	(omitted)
(deleted)	(deleted)	(deleted)
(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)	(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	The metabolism of these drugs is suppressed by the inhibitory activity of lonafarnib against CYP3A.

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		be considered as necessary.	
	Adrenocorticosteroids	(omitted)	(omitted)
	(omitted)	(omitted)	(omitted)