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Report on Investigation Results

August 17, 2022

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	a. Riociguat b. Ritonavir c. Lopinavir/ritonavir d. Atazanavir sulfate
[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 approval application was made to add the indication of “pulmonary arterial hypertension (PAH)” (hereinafter referred to as “PAH”).

Although no results from the pharmacokinetic studies of riociguat had been obtained for co-administration of riociguat and human immunodeficiency virus (hereinafter referred to as “HIV”) protease inhibitors (ritonavir, atazanavir, etc.) at the time of the initial approval review of riociguat, the co-administration has been contraindicated for the following reasons:

- Riociguat is mainly metabolized by CYP1A1, CYP2C8, CYP2J2, and CYP3A, and it is a substrate of P-glycoprotein (hereinafter referred to as “P-gp”) and breast cancer

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resistance protein (hereinafter referred to as “BCRP”).

- In the 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 concomitant use with ketoconazole to those after administration of riociguat alone were 1.4603 [1.3529-1.5763] and 2.5014 [2.1406-2.9229], respectively.
- Based on the above knowledge, it is considered that a similar increase in riociguat exposure may occur in concomitant use with HIV protease inhibitors that inhibit multiple CYP isoforms, P-gp and BCRP, as observed in the concomitant use with ketoconazole.

Recently, the results of clinical trials investigating the pharmacokinetic drug-drug interactions between riociguat and anti-HIV drugs including HIV protease inhibitors and *in vitro* studies investigating the inhibitory activities of anti-HIV drugs against CYP isoforms were submitted to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) by the marketing authorization holder (MAH) of riociguat. On the basis of these study results, PMDA decided to conduct an investigation regarding the necessity of the contraindications for co-administration of riociguat and HIV protease inhibitors.

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 PMDA

Currently, co-administration with HIV protease inhibitors (ritonavir, lopinavir/ritonavir, indinavir, atazanavir, saquinavir) is contraindicated in the Precautions of riociguat. Among these HIV protease inhibitors, preparations containing ritonavir (ritonavir, lopinavir/ritonavir) and atazanavir were reviewed in this investigation. Regarding indinavir and saquinavir, the statement will be deleted from the Precautions of riociguat because of discontinuation of marketing (completion of period of transitional measures). Therefore, concomitant use with these drugs was not investigated.

CYP1A1 and CYP3A4 are shown to be important for the clearance of riociguat (See section 1.3). For lopinavir/ritonavir, inhibitory activity against CYP3A4 is shown to be low

when lopinavir and ritonavir are combined compared to ritonavir alone,[1] and also, no data indicating that lopinavir inhibits CYP1A1 have been obtained. Taking account of this, the investigation on the necessity of contraindications for co-administration of riociguat with lopinavir/ritonavir was conducted based mainly on the information of ritonavir.

1. Pharmacokinetics

1.1 Pharmacokinetic interaction of riociguat and antiretroviral combination regimens in HIV-1-infected adults (Study 17957: Clinical Trial Reports, Pulm Circ. 2019; 9: 1-10)

Pharmacokinetics and safety of riociguat were investigated when a single oral dose of riociguat 0.5 mg was administered in the fasted state in non-Japanese HIV patients without PAH who had been receiving anti-HIV drugs at a fixed dose for 6 weeks or longer (target sample size: 40 cases in total consisting of 8 cases in each group). The following 5 groups were specified as anti-HIV drugs to be used in combination: (1) Efavirenz/emtricitabine/tenofovir (Atripla (unapproved in Japan)) combination group, (2) emtricitabine/rilpivirine/tenofovir (Complera Combination Tablets) combination group, (3) elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild Combination Tab.) combination group, (4) abacavir/dolutegravir/lamivudine (Triumeq Combination Tablets) combination group, (5) ritonavir-boosted triple regimen group.

Of 47 cases registered in the study, 41 cases were included in the safety analysis, and 40 cases were included in the pharmacokinetic analysis excluding 1 case (ritonavir-boosted triple regimen group) in which deviation on sampling procedure was observed. One case in efavirenz/emtricitabine/tenofovir combination group, 2 cases in abacavir/dolutegravir/lamivudine combination group, and 1 case in ritonavir-boosted triple regimen group were smokers, all of which were included in the safety and pharmacokinetic analyses.

The pharmacokinetic parameters of riociguat in each combination group are shown in Table 1. Among 8 cases in the ritonavir-boosted triple regimen group, AUC and C_{max} of riociguat were 39.8 μg·h/L and 8.94 μg/L, respectively in the 1 case in which atazanavir was co-administered in addition to ritonavir.

[1] Summaries of product application (https://www.pmda.go.jp/drugs/2000/g001213/index.html (accessed on July 14, 2022))

Table 1. Pharmacokinetic parameters of riociguat after a single dose of riociguat in combination with anti-HIV drugs

	Efavirenz /emtricitabine /tenofovir combination group (8 cases)	Emtricitabine /rilpivirine /tenofovir combination group (8 cases)	Elvitegravir /cobicistat /emtricitabine /tenofovir combination group (8 cases)	Abacavir /dolutegravir /lamivudine combination group (8 cases)	Ritonavir-boosted triple regimen group* (8 cases)
AUC (μg·h/L)	95.5 (105)**	185 (103)	185 (74.1)	255 (65.8)	116 (74.6)
C_{max} (μg/L)	14.2 (56.3)	16.3 (23.0)	20.4 (25.9)	20.0 (46.4)	15.8 (41.0)

Geometric mean value (% CV value)

AUC: Area under the plasma concentration-time curve (extrapolated value to infinity), C_{max}: Maximum plasma concentration

* 7 cases receiving riociguat in combination with ritonavir/darunavir/emtricitabine/tenofovir and 1 case receiving riociguat in combination with atazanavir/ritonavir/emtricitabine/tenofovir were included. **n=7

1.2 Comparison of pharmacokinetics of riociguat with or without co-administration with anti-HIV drugs (Study 18634: Clinical Trial Reports, Pulm Circ. 2019; 9: 1-10)

By using the results of previous clinical trials that examined the pharmacokinetics of riociguat when riociguat was administered alone as a historical control and comparing with the results of the drug-drug interaction study of riociguat and anti-HIV drugs (Study 17957), the pharmacokinetic interactions between riociguat and anti-HIV drugs were investigated. As a historical control, data of 40 cases in total (Study 11261: 16 cases; Study 13009: 24 cases) in which a single dose of riociguat 0.5 mg alone was administered in Study 11261 (administration in the fed state) or Study 13009 (administration in the fasted state) were used. The summary of Study 11261 and Study 13009 is shown in Table 2.

Table 2. Summary of Study 11261 and Study 13009

Study name	Administration timing	Number of cases	Summary of the studies
Study 11261	Fed state	16 cases (3 smokers, 13 non-smokers)	Drug-drug interaction study with ketoconazole. A single oral dose of 0.5 mg of riociguat was administered in the fed state in 16 non-Japanese healthy adult subjects in the administration period A. Subsequently, in the administration period B, a single oral dose of 0.5 mg of riociguat was co-administered with 400 mg of ketoconazole in the fed state after an oral dose of 400 mg ketoconazole was administered once-daily for 4 days.
Study 13009	Fasted state	24 cases (7 smokers, 17 non-	A clinical trial investigating the dose proportionality in riociguat pharmacokinetics. In the crossover trial with 24 non-Japanese healthy adult subjects, single oral doses of 0.5, 1.0, 1.5, 2.0, and 2.5 mg of

		smokers)	riociguat were administered in fasted state in each period (with approximately 1-week washout period).

The ratios of AUC of riociguat co-administered with anti-HIV drugs versus that of riociguat alone, using Study 11261 and Study 13009 (administration in the fed state and in the fasted state, respectively) as a historical control, are shown in Table 3. The ratios of C_{max} were not calculated because C_{max} of riociguat has been shown to be affected by meals.

Table 3. The ratios of AUC of riociguat co-administered with anti-HIV drugs versus that of riociguat alone (administration in fed state and in fasted state)

	Efavirenz /emtricitabine/tenofovir combination group (7 cases)	Emtricitabine /rilpivirine /tenofovir combination group (8 cases)	Elvitegravir /cobicistat /emtricitabine/tenofovir combination group (8 cases)	Abacavir /dolutegravir/lamivudine combination group (8 cases)	Ritonavir-boosted triple regimen group (8 cases)
AUC ratio	1.0639 (0.6197, 1.8263)	2.0617 (1.2368, 3.4367)	2.0647 (1.2386, 3.4418)	2.8402 (1.7038, 4.7345)	1.2900 (0.7739, 2.1504)

The ratios of the least squares means (90% confidence interval)

Also, the ratios of AUC and C_{max} of riociguat co-administered with anti-HIV drugs versus those of riociguat alone using only Study 13009 (administration in the fasted state) as a historical control are shown in Table 4.

Table 4. The ratios of AUC and C_{max} of riociguat co-administered with anti-HIV drugs versus those of riociguat alone (administration in fasted state)

	Efavirenz /emtricitabine/ tenofovir combination group (7 cases)	Emtricitabine /rilpivirine /tenofovir combination group (8 cases)	Elvitegravir /cobicistat /emtricitabine/ tenofovir combination group (8 cases)	Abacavir /dolutegravir/ lamivudine combination group (8 cases)	Ritonavir-boosted triple regimen group (8 cases)
AUC ratio	0.9703 (0.5414, 1.7390)	1.8803 (1.0799, 3.2738)	1.8831 (1.0816, 3.2786)	2.5903 (1.4877, 4.5099)	1.1765 (0.6757, 2.0485)
C_{max} ratio	0.8955 (0.6728, 1.1919)	1.0299 (0.7738, 1.3708)	1.2859 (0.9661, 1.7116)	1.2657 (0.9509, 1.6847)	1.0006 (0.7517, 1.3318)

The ratios of least squares means (90% confidence interval)

The MAH of riociguat explained the appropriateness of comparing Study 17957, Study

11261, and Study 13009 as follows:

As a result of the population pharmacokinetic analysis (hereinafter referred to as “PPK analysis”) that was conducted using the data of phase III studies in patients with PAH and with CTEPH, the final model of pharmacokinetics of riociguat was shown in an oral 1-compartmental model with apparent total body clearance (hereinafter referred to as “CL/F”), apparent volume of distribution (hereinafter referred to as “V/F”) and the primary absorption rate constant as parameters. Creatinine clearance, bilirubin, smoking habit, and concomitant use of bosentan were selected as the covariates of CL/F, and body weight as the covariate of V/F.

The age, body weight, and BMI of the subjects were comparable among the 3 studies. The distributions of gender and race were different among the studies; however, they were not selected as the covariates of the final model of PPK analysis. Therefore, it is considered that they do not have a major impact on the pharmacokinetics of riociguat. Smoking was the covariate of CL/F; however, there was no marked difference in the proportion of smokers among the studies. Also, creatinine clearance and bilirubin, which reflect renal and liver function, respectively, were covariates of CL/F. Although creatinine clearance was not measured in any of these studies, the serum creatinine, serum urea nitrogen, and bilirubin values at screening suggested that there was no clear difference in the pharmacokinetic evaluation of riociguat among the subjects in 3 studies in terms of their renal and liver function.

For study design, preparations used in each study, and the evaluation method of pharmacokinetics (timing of blood sampling, measurement method of riociguat concentration, calculation method of pharmacokinetic parameters), there was also no clear difference which might impair the comparability of the pharmacokinetics among the studies.

Based on the above, the MAH of riociguat considered it appropriate to compare the results of Study 17957 with those of Study 11261 and Study 13009, which were treated as historical controls.

1.3 *In vitro* study (KINM 170163-ELB; Clinical Trial Reports, Expert Opin Drug Metab Toxicol. 2019; 15: 975-84)

Regarding the increase in exposure of riociguat in concomitant use with anti-HIV drugs in Study 17957, 2 *in vitro* studies (one using recombinant human CYP isoforms, the other using human hepatocytes) were conducted to investigate pharmacokinetic mechanisms.

In the study using recombinant human CYP isoforms, by incubating riociguat with recombinant human CYP1A1 and CYP3A4 (20 minutes for CYP1A1, 60 minutes for CYP3A4) in the presence (maximum concentration 50 µM) or absence of each active ingredient of anti-HIV drugs and measuring the concentrations of riociguat and major metabolite M-1, the concentration required for 50% inhibition of CYP1A1 or CYP3A4 by each active ingredient and inhibition constant (hereinafter referred to as "Ki value") were calculated. Also, on the basis of Ki values and the estimated concentration of each active ingredient of the anti-HIV drugs as well as the estimated fraction metabolized of riociguat by CYP1A1 and CYP3A4, the AUC ratio of riociguat in combination with anti-HIV drugs (single active ingredient or combination of multiple active ingredients[2]) versus riociguat alone *in vivo* was estimated.

In the study using human hepatocytes, by incubating riociguat (up to 180 minutes) with human hepatocytes in the presence or absence of anti-HIV drugs (combination of multiple active ingredients[2]) and measuring the concentrations of riociguat and the major metabolite M-1, intrinsic hepatic clearance of riociguat and the hepatic blood clearance ratio of the riociguat clearances with and without anti-HIV drugs (hereinafter referred to as "CL_h ratio") were calculated. Similarly, the CL_h ratio of CYP1A1 substrate (granisetron: Metabolism to 7-hydroxygranisetron) and CYP3A4 substrate (midazolam: Metabolism to 1-hydroxymidazolam) was calculated. In addition, the ratio of AUC of riociguat co-administered with anti-HIV drugs (combination of multiple active ingredients) versus that of riociguat alone was estimated based on the intrinsic hepatic clearance of riociguat.

On the basis of the results of these *in vitro* studies, etc., the MAH of riociguat explained as follows:

- The CL_h ratio of riociguat obtained in the study using human hepatocytes was correlated with the CL_h ratio of CYP1A1 substrate (correlation coefficient r = 0.96, coefficient of determination r^2 = 0.92); however, it was not correlated with the CL_h ratio of CYP3A4 substrate (r = -0.31, r^2 = 0.10). The dominant role of CYP1A1 was confirmed in the metabolic clearance of riociguat.
- On the basis of the *in vitro* studies investigating the inhibitory activity of each active

[2] Types of combination of multiple ingredients are the following six types which were used in the Study 17957: (1) efavirenz/emtricitabine/tenofovir, (2) emtricitabine/rilpivirine/tenofovir, (3) elvitegravir/cobicistat/emtricitabine/tenofovir, (4) abacavir/dolutegravir/lamivudine, (5) ritonavir/darunavir/ emtricitabine/tenofovir,(6) atazanavir/ritonavir/emtricitabine/tenofovir.

ingredient contained in anti-HIV drugs against CYP1A1 and CYP3A4, the estimated AUC ratio of riociguat in concomitant use with each active ingredient contained in anti-HIV drugs that was examined in Study 18634 as well as the degree of increase in AUC in concomitant use with each anti-HIV drug compared to that of riociguat alone in Study 18634, the increase in riociguat exposure in concomitant use with anti-HIV drugs in Study 18634 could be reasonably explained by the CYP inhibitory activity of the active ingredients contained in anti-HIV drugs as shown below.

- Emtricitabine/rilpivirine/tenofovir combination group: Rilpivirine
- Elvitegravir/cobicistat/emtricitabine/tenofovir combination group: Cobicistat
- Abacavir/dolutegravir/lamivudine combination group: Abacavir
- Ritonavir-boosted triple regimen[3] group: Ritonavir

Regarding the interactions of anti-HIV drugs with riociguat mediated by P-gp and BCRP, no examination has been made in an *in vitro* study. However, the MAH of riociguat explained that the possibility that the exposure of riociguat would increase to a clinically meaningful level by the inhibition of P-gp and BCRP by anti-HIV drugs would be low for the following reasons:

- Riociguat is a substrate of P-gp and BCRP; however, 4 to 19% of a riociguat dose is eliminated unchanged in urine by glomerular filtration[4], and the contribution of active renal secretion by P-gp and BCRP is not considered likely.
- Absolute bioavailability of riociguat is approximately 94%, and the effect on the pharmacokinetics of riociguat by inhibition of P-gp and BCRP in the digestive tract is considered to be limited.

2. Safety

2.1 Post-marketing clinical study (Study 17957)

In a study on drug interactions between riociguat and anti-HIV drugs in HIV patients (Study 17957), of the 47 cases registered in the study, 41 subjects who received the single dose of riociguat were included in the safety analysis. Adverse events reported by at least 1 patient in any group are shown in Table 5. Of the 15 adverse events observed in this study, 1

[3] Ritonavir/darunavir/ emtricitabine/tenofovir combination or atazanavir/ ritonavir/ emtricitabine/tenofovir combination (See Table 1)
[4] Clinical Pharmacokinetic and Pharmacodynamic Profile of Riociguat. (Clin Pharmacokinet. 2018; 57: 647-661.)

headache in the emtricitabine/rilpivirine/tenofovir combination group and 2 headaches and 1 upper abdominal pain in ritonavir-boosted triple regimen group were considered to be related to riociguat by the investigators.

No severe or serious adverse events, adverse events leading to outcome of death or treatment discontinuation were observed in this study.

Table 5. Adverse events reported by at least 1 patient in any group

	Efavirenz/ emtricitabine/ tenofovir combination group (8 cases)	Emtricitabine/ rilpivirine/ tenofovir combination group (8 cases)	Elvitegravir/ cobicistat/ emtricitabine/ tenofovir combination group (8 cases)	Abacavir/ dolutegravir/ lamivudine combination group (8 cases)	Ritonavir-boosted triple regimen group* (9 cases)
Headache	0	1 (12.5)	0	1 (12.5)	2 (22.2)
Fatigue	0	0	1 (12.5)	1 (12.5)	0
Diarrhoea	0	0	0	0	1 (11.1)
Dizziness	0	0	1 (12.5)	0	0
Lip swelling	0	0	1 (12.5)	0	0
Oral paraesthesia	1 (12.5)	0	0	0	0
Oropharyngeal pain	0	1 (12.5)	0	0	0
Pain	0	1 (12.5)	0	0	0
Fever	0	0	0	1 (12.5)	0
Upper abdominal pain	0	0	0	0	1 (11.1)
Urethritis	0	1 (12.5)	0	0	0

Number of cases (%)

* 7 cases receiving riociguat in combination with ritonavir/darunavir/emtricitabine/tenofovir and 2 cases receiving riociguat in combination with atazanavir/ritonavir/emtricitabine/tenofovir were included.

2.2 Adverse event case reports

For cases of serious adverse events from clinical trials and adverse events from post-marketing data sources, both of which have been obtained by the MAH of riociguat, a total of 30 cases, 29 overseas and 1 in Japan, were identified as a result of searching for suspected concomitant use of anti-HIV drugs using the Anatomical Therapeutic Chemical Classification (ATC) or the WHO Drug Dictionaries Drug Code corresponding to anti-HIV drugs (data lock: March 6, 2022). No adverse events were observed in the 30 cases that were suspected to have been caused by the concomitant use of riociguat and anti-HIV drugs. Six hypotension-related events (4 hypotension and 2 decreased blood pressure)

were observed in 5 of 30 cases, including 1 case of serious hypotension (Appendix 2).

The MAH of riociguat explained that concurrent events (diarrhoea), patient predisposition (atrial fibrillation, cardiac failure), and concomitant drugs (antihypertensives) may have contributed to the occurrence of serious hypotension.

3. Published literature on the safety of concomitant use of riociguat and anti-HIV drugs

The following 2 published articles were retrieved from a survey of published literature[5] referring to the concomitant use of riociguat and anti-HIV drugs, in order to investigate the safety when riociguat is co-administered with anti-HIV drugs. In these published articles, there were no new safety concerns regarding the concomitant use of riociguat and anti-HIV drugs. The summaries are as follows.

(1) Cor Pulmonale from Concomitant Human Immunodeficiency Virus Infection and Methamphetamine Use (CASE (Phila). 2021; 5: 239-42)

This case report demonstrates development of serious PAH and cor pulmonele by HIV infection and long-term use of methamphetamine. The case report states that the patient took highly active antiretroviral therapy (HAART), started PAH medical therapy 4 years prior to the current presentation to the authors' emergency department, and had discontinued his PAH medications (riociguat, selexipag, and ambrisentan) because of nausea and vomiting 3 weeks before the current presentation. However, there were no descriptions of interactions between riociguat and anti-HIV drugs.

(2) *In vitro- in vivo* correlation of the drug-drug interaction potential of antiretroviral HIV treatment regimens on CYP1A1 substrate riociguat (Expert Opin Drug Metab Toxicol. 2019; 15: 975-84)

This article was a report on the *in vitro* study stated in the section 1.3.

4. Statements in Japanese and overseas clinical practice guidelines

The results of the review of the statements in the guidelines for pulmonary hypertension and HIV infection on the safety concerning the concomitant use of riociguat and HIV protease

[5] Using the Embase and the database of the MAH of riociguat, we searched for published literature mentioning the concomitant use of riociguat and anti-HIV drugs by search terms including non-proprietary name (search date: March 6, 2022).

inhibitors are as follows.

(1) Guidelines for Treatment of Pulmonary Hypertension (2017 edition) (The Japanese Circulation Society, Japanese Pulmonary Circulation and Pulmonary Hypertension Society, etc.)

The guidelines state that when pulmonary hypertension drugs are co-administered with protease inhibitors, which are anti-HIV drugs, the blood concentration of the former may increase due to the CYP3A4 inhibitory effect of the latter, and riociguat and preparations containing ritonavir are contraindicated for co-administration.

(2) HIV Treatment Guidelines (March, 2022 edition) (FY 2021, Health, Labour and Welfare Sciences Research Grants, Research project on HIV/AIDS, Study group with the aim of establishing team medical care and improving healthcare standards in HIV infections and hemophilia)

No particular mention was found regarding the concomitant use of riociguat and anti-HIV drugs.

5. Current description of overseas package inserts

The results of the review of the package inserts in the US, the EU, the UK, Canada, and Australia are as follows.

5.1 Riociguat

The current description of overseas package inserts of riociguat is shown in Table 1 in Appendix 3.

No package inserts for overseas countries or regions list HIV protease inhibitors and riociguat as contraindications for co-administration. Overseas package inserts state the following: In order to mitigate the risk of hypotension associated with increased exposure to riociguat, the starting dose at 0.5 mg 3 times a day when initiating concomitant use of riociguat should be considered in patients receiving strong inhibitors of CYP and P-gp/BCRP including HIV protease inhibitors. Signs and symptoms of hypotension should be monitored during concomitant use. If patients develop signs or symptoms of hypotension, a dose reduction should be considered.

In addition, the package inserts of the EU, the UK, Canada, and Australia state that in

patients on stable doses of riociguat, the initiation of strong inhibitors of CYP, P-gp and BCRP is not recommended because no dosage recommendation can be given due to limited data, and that alternative treatments should be considered.

5.2 HIV protease inhibitors, etc.

5.2.1 Preparations containing ritonavir

The current description of overseas package inserts of preparations containing ritonavir is shown in in Table 2 in Appendix 3.

There was no statement of concomitant use of either ritonavir or lopinavir/ritonavir with riociguat in the package inserts of the US, Canada, and Australia. Although riociguat is not contraindicated for co-administration in the EU and UK package inserts, the co-administration of riociguat with ritonavir or lopinavir/ritonavir is not recommended since serum concentrations of riociguat may be increased due to the CYP3A and P-gp inhibitory effect by ritonavir or lopinavir/ritonavir.

5.2.2 Atazanavir

The descriptions of atazanavir in the overseas package inserts are shown in Table 3 in Appendix 3. None of them stated concomitant use with riociguat.

Of note, the current description of the anti-HIV drugs other than HIV protease inhibitors used in Study 17957 (efavirenz, emtricitabine, tenofovir, rilpivirine, elvitegravir, cobicistat, abacavir, dolutegravir, lamivudine) was reviewed in overseas package inserts. None of them were contraindicated for co-administration with riociguat.

IV. PMDA's judgment based on the investigation results

PMDA considers it acceptable to allow the concomitant use of riociguat with preparations containing ritonavir or atazanavir on the premise that measures (starting at a lower dose than 1.0 mg of riociguat 3 times a day should be considered, etc.) are taken to minimize the risk of hypotension, etc. associated with the increased exposure to riociguat due to the drug interactions for the following reasons.

- In Study 18634, it was shown that the exposure of riociguat was increased by approximately 1.3-fold when it was co-administered with ritonavir and/or atazanavir

compared to the historical data of riociguat administered alone. Given the degree of this increase in exposure, it should be possible to ensure a margin of safety by starting riociguat at a lower dose than the usual starting dose, since riociguat is a drug that is started at a low dose and titrated according to the patient's condition.

- In the overseas package inserts (the US, the EU, the UK, Canada, and Australia), concomitant use of riociguat with HIV protease inhibitors is not contraindicated. Overseas adverse event reports and published literature, etc. did not identify any particular clinical concerns regarding the concomitant use of riociguat with HIV protease inhibitors including ritonavir and atazanavir.
- In Study 17957, no particular safety problems were observed when riociguat was co-administered with ritonavir or atazanavir, although the study was conducted with a small number of patients.

Of note, higher AUC ratios were observed in the emtricitabine/rilpivirine/tenofovir combination group, elvitegravir/cobicistat/emtricitabine/tenofovir combination group, and abacavir/dolutegravir/lamivudine combination group in Study 17957 than in the ritonavir-boosted triple regimen group, and the CYP inhibitory effects of rilpivirine, cobicistat and abacavir are suggested to be responsible for the increased exposure in each group. Given the degree of increased exposure in each group and the fact that riociguat is a drug that should be started at a low dose and titrated according to the patient's condition, PMDA considered that there is little need to contraindicate the concomitant use of these drugs (rilpivirine, cobicistat or abacavir) with riociguat and that this should be specified in Precautions for Co-administration, as with HIV protease inhibitors. PMDA intends to take these measures separately.

V. Expert discussion

The PMDA's conclusion that it is acceptable to allow the concomitant use of riociguat with atazanavir or preparations containing ritonavir, on the premise that measures are taken to minimize the risk of hypotension due to the drug interaction (e.g., starting at a lower dose than 1.0 mg of riociguat 3 times a day, etc.) was supported by all the expert advisors after the following comments were made:

- There have been no cases in which riociguat was actually used in combination with anti-

HIV drugs in the Japanese population. Therefore, it is necessary to continue to collect information regarding safety data on co-administration of riociguat and anti-HIV drugs and to appropriately provide information to healthcare professionals.

- In clinical settings, it is possible that an option of starting administration of riociguat at a lower dose than the usual dose may not be recognized. Regarding the risk minimization measures, it is necessary to appropriately provide information to healthcare professionals by using the materials, etc.

Considering the above opinions, PMDA instructed the MAH of riociguat to provide information to call for further attention to healthcare professionals regarding the measures to minimize the risk of hypotension, etc. due to the drug interaction, as well as to collect and evaluate safety information of the cases in which riociguat is co-administered with preparations containing ritonavir or with atazanavir after the revisions of Precautions.

The MAH of riociguat responded as follows: Information to call further attention will be provided to healthcare professionals at the time of revising the Precautions. Also, detailed data on co-administration of riociguat with preparations containing ritonavir or with atazanavir and incidences of adverse drug reactions, etc. in the cases of co-administration will be collected and analyzed, and the effect of this measure will be reviewed and evaluated after taking the measure.

In addition, some expert advisors commented that if the language “starting at a lower dose than 1.0 mg of riociguat 3 times a day should be considered” is used as a precautionary statement when riociguat is co-administered with preparations containing ritonavir or with atazanavir, it would be hard to understand and may lead to misunderstanding in clinical settings. Therefore, it is recommended that the information “0.5 mg of riociguat 3 times a day” should be included for the precautionary statement in the Precautions of riociguat.

Taking into account the above opinions, PMDA considers it appropriate to clarify that starting at a dose of 0.5 mg 3 times a day should be considered for the precautionary statement in the Precautions of riociguat. The review report of riociguat states that it was observed that AUC of riociguat in patients with renal impairment (creatinine clearance between 15 and 80 mL/min) increased by approximately 2-fold compared to that in subjects with normal renal function, and therefore, in addition to other reasons, it is recommended to

also consider starting at a dose of 0.5 mg 3 times a day. Taking account of this, it should be appropriate to clarify that starting at a dose of 0.5 mg 3 times a day should also be considered for a precautionary statement for patients with renal impairment in the Precautions.

Regarding the PMDA's decision that rilpivirine, cobicistat, and abacavir should be specified in Precautions for Co-administration, one expert advisor commented that it is necessary to consider whether concomitant use of riociguat and abacavir should be contraindicated because the exposure of riociguat increased by approximately 2.5-fold in combination with abacavir.

Given these opinions, PMDA reviewed the necessity that concomitant use of riociguat and abacavir should be contraindicated. Considering that exposure of riociguat increased by approximately 2.5-fold in combination with abacavir, it is expected that the exposure when riociguat is started at a lower dose than the usual starting dose (0.5 mg 3 times a day) in patients treated with abacavir will be higher than the exposure when riociguat is started at the usual dose (1 mg 3 times a day) in the patients untreated with abacavir. However, it is considered that the necessity for contraindicating concomitant use is low taking into account that no particular problems were observed for the concomitant use in the adverse event reports, published literature, etc., although co-administration of riociguat and abacavir is not contraindicated in Japan and overseas, and no particular safety problems were observed when riociguat was co-administered with abacavir in Study 17957. Note, however, that considering the Study 17957 was conducted with a small number of patients, PMDA concluded that it is appropriate to continue to collect safety information for the concomitant use of riociguat and anti-HIV drugs including abacavir and to consider the necessity of additional measures.

VI. Overall evaluation

PMDA concluded that Precautions may be revised according to Appendix 4 based on the above discussions.

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Appendix 1

Summary of drug products investigated

	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 ·Inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or postoperative persistent or recurrent 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 <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 it is not tolerated (e.g., occurrence of signs or symptoms of hypotension), the dose should be reduced by 0.5 mg per dose.
b.	Ritonavir	Norvir Tablets 100 mg	AbbVie GK	Indications HIV infection

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	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				Dosage and administration The usual adult dosage is 600 mg of ritonavir (6 tablets) orally administered twice a day after a meal. A dose of 300 mg twice a day should be administered after a meal on the first day of administration, a dose of 400 mg twice a day on the second and third day, a dose of 500 mg twice a day on the fourth day, and a dose of 600 mg twice a day on the fifth day and thereafter. This drug must be used in combination with other anti-HIV drugs.
c.	Lopinavir/ritonavir	Kaletra Combination Tablets, Kaletra Combination Oral Solution	AbbVie GK	Indications HIV infection Dosage and administration <Kaletra Combination Tablets> The usual adult dosage is 400 mg/100 mg of lopinavir/ritonavir (2 tablets) orally administered twice a day or 800 mg/200 mg of lopinavir/ritonavir (4 tablets) orally administered once a day. For children with a body weight of greater than 40 kg, a dose of 400 mg/100 mg as lopinavir/ritonavir (2 tablets) can be orally administered twice a day. This drug can be administered with or without food. <Kaletra Combination Oral Solution> The usual adult dosage is 400 mg/100 mg of lopinavir/ritonavir (5 mL) orally administered twice a day after a meal. The usual child dosage is 12 mg/3 mg per kg body mass for children weighing between 7 kg and 15 kg, and 10 mg/2.5 mg per kg body mass for children weighing between 15 kg and 40 kg, orally administered twice a day after a meal. The maximum daily dose should be 400 mg/100 mg (5 mL) administered twice a day.

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	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
d.	Atazanavir sulfate	Reyataz Capsules 150 mg, 200 mg	Bristol-Myers Squibb K.K.	Indications HIV-1 infection Dosage and administration The usual adult dosage is orally administered during or immediately after a meal according to the dosage and administration shown below. This drug must be used in combination with other anti-HIV drugs. <Anti-HIV drug treatment-naive patients> ·300 mg of atazanavir and 100 mg of ritonavir orally co-administered once a day. ·400 mg of atazanavir orally administered once a day. <Anti-HIV drug treatment-experienced patients> ·300 mg of atazanavir and 100 mg of ritonavir orally co-administered once a day.

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Appendix 2

Table　Occurrence of adverse events involving hypotension in patients with suspected co-administration of riociguat and anti-HIV drugs

No.	Country	Age	Sex	Concomitant anti-HIV drugs	Adverse event	Seriousness	Outcome
1	US	47	Male	Dolutegravir/etravirine	Decreased blood pressure	Serious	Not recovered
2	US	53	Male	Combination of anti-virus agents for the treatment of HIV infection	Hypotension	Non-serious	—
					Hypotension	Non-serious	—
3	US	—	—	Ritonavir	Hypotension	Non-serious	Unknown
4	US	49	Female	Dolutegravir sodium	Decreased blood pressure	Non-serious	Resolving
5	Germany	55	Male	Dolutegravir sodium/emtricitabine/tenofovir alafenamide fumarate	Hypotension	Non-serious	—

—: No information

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Appendix 3

Table 1 Related description of riociguat for concomitant use with anti-HIV drugs in overseas package inserts

Country/region	Brand name (Version of package insert)	Description
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

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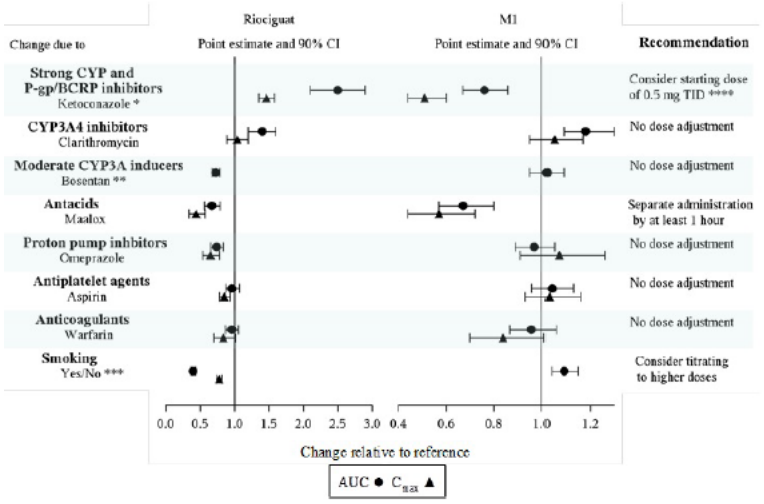
		hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]. **12 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. **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)].*
EU	ADEMPAS	**4.3 Contraindications**

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	(February, 2022)	(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 When initiating Adempas in patients on stable doses of 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), 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 sections 4.4 and 4.5). **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 Adempas 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 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 Interaction with other medicinal products and other forms of interaction** Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors Highly active antiretroviral therapy (HAART) In vitro, abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In addition, ritonavir showed inhibition of P-gp.

		The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a dedicated study in HIV patients. 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. To mitigate the risk of hypotension when Adempas 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).
UK	ADEMPAS (December, 2021)	**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 When initiating Adempas in patients on stable doses of 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), 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 sections 4.4 and 4.5). **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 Adempas 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).

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		• 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 Interaction with other medicinal products and other forms of interaction** Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors Highly active antiretroviral therapy (HAART) In vitro, abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In addition, ritonavir showed inhibition of P-gp. The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a dedicated study in HIV patients. 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. To mitigate the risk of hypotension when Adempas is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and Pgp/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).
Canada	ADEMPAS (March, 2020)	**CONTRAINDICATIONS** (No related description) **WARNINGS AND PRECAUTIONS** <u>Hypotension</u> As a sGC stimulator, ADEMPAS acts as a vasodilator, lowering both pulmonary and systemic blood pressure. The demonstrated risk of hypotension should be carefully considered (see ADVERSE REACTIONS), in particular in patients with concomitant or underlying conditions such as low systemic blood pressure (e.g., systolic blood pressure < 95 mmHg), coronary artery disease (CAD), hypovolemia, resting hypotension, severe left ventricular outflow obstruction, autonomic dysfunction, as well as in patients on concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors (see WARNINGS and PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors).

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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 DRUG INTERACTIONS, 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 DOSAGE AND ADMINISTRATION, Strong CYP and P-gp/BCRP Inhibitors and DRUG INTERACTIONS, 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.

DRUG INTERACTIONS

Overview

Effects of Riociguat on Other Substances

Effects of Other Substances on Riociguat

ADEMPAS is cleared mainly via biliary/direct fecal excretion of the unchanged drug, and renal excretion of the unchanged drug via glomerular filtration. ADEMPAS is mainly catalysed to its main metabolite M1 by several CYP isoforms (CYP1A1, CYP2J2, CYP3A4, CYP3A5). Based on in vitro studies, riociguat was found to be a substrate for the membrane transport proteins P-gp/BCRP. Inhibitors or inducers of these enzymes or transporters may affect riociguat exposure.

Riociguat exhibits a reduced solubility at neutral pH vs. acidic medium. Co-medication of drugs increasing the upper gastro-intestinal pH may lead to lower oral bioavailability.

Drug-Drug Interactions

Table 5: Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Highly active antiretroviral therapy	I, CT	In vitro, abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited	Due to limited clinical experience, ADEMPAS and multi pathway CYP

		(HAART) including HIV protease inhibitors		CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In vitro, riociguat main metabolite M1 formation in human liver microsomes was considerably inhibited by HIV protease inhibitors (ritonavir, atazanavir > indinavir, IC50 values of 5.3 to 11.7 μM). Ritonavir and saquinavir showed inhibitory potency on P-gp/BCRP mediated efflux of riociguat in vitro ([I1]/IC50 >0.1 or [I2]/IC50>10). The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a pharmacokinetic drug-drug interaction study with HIV non-PAH patients. Concomitant administration of a stable regimen of varying HAART combinations with a single 0.5 mg dose of ADEMPAS led to an increase in ADEMPAS mean AUC and Cmax of up to about 160% and 29%, respectively in HIV non-PAH patients compared to a healthy historical control group. No new safety findings were observed in this single dose	or P-gp/BCRP inhibitors should be co-administered with caution. When initiating ADEMPAS treatment in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. as contained in HAART therapy, 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 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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		study. **DOSAGE AND ADMINISTRATION** 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 DRUG INTERACTIONS, Drug-Drug Interactions). Consider a starting dose of 0.5 mg, three times a day 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 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors and DRUG INTERACTIONS, Drug-Drug Interactions).
Australia	ADEMPAS	**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 Sections 4.2 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

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		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 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 Effects of Other Substances on ADEMPAS Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, CYP2C8, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of the unchanged drug, and renal excretion of the unchanged drug via glomerular filtration. Based on in vitro studies, riociguat was found to be a substrate for the membrane transport proteins P-gp/BCRP. Inhibitors or inducers of these enzymes or transporters may affect riociguat exposure. Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors Highly active antiretroviral therapy (HAART) In vitro, rilpivirine, abacavir, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with rilpivirine as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In addition, ritonavir showed inhibition of P-gp. The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a dedicated study in HIV patients. Concomitant administration of HAART combinations led to an increase in riociguat

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		mean AUC of up to about 160% and up to an approximate 29% 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. When initiating ADEMPAS treatment in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. as contained in HAART therapy, 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 Sections 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.

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Table 2　Related description for concomitant use with riociguat in overseas package inserts of preparations containing ritonavir

Country/region	Brand name (Version of package insert)	Description
Ritonavir		
US	NORVIR (October, 2020)	(No related description)
EU	NORVIR (March, 2021)	**4.3 Contraindications** (No related description) **4.4 Special warnings and precautions for use** Interactions with other medicinal products Riociguat The concomitant use of ritonavir is not recommended due to potential increase in riociguat exposure (see section 4.5). **4.5 Interaction with other medicinal products and other forms of interaction** Medicinal product that are affected by the use of ritonavir Riociguat Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with Norvir is not recommended (see section 4.4 and refer to riociguat SmPC).
UK	NORVIR (January, 2021)	**4.3 Contraindications** (No related description) **4.4 Special warnings and precautions for use** Interactions with other medicinal products Riociguat The concomitant use of ritonavir is not recommended due to potential increase in riociguat exposure (see section 4.5).

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		4.5 Interaction with other medicinal products and other forms of interaction Medicinal product that are affected by the use of ritonavir Riociguat Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with Norvir is not recommended (see section 4.4 and refer to riociguat SmPC).
Canada	NORVIR (July, 2021)	(No related description)
Australia	NORVIR (July, 2020)	(No related description)
Lopinavir/ritonavir		
US	KALETRA (October, 2020)	(No related description)
EU	KALETRA (May, 2021)	**4.3 Contraindications** (No related description) **4.4 Special warnings and precautions for use** Interactions with other medicinal products The combination of Kaletra with: - riociguat is not recommended (see section 4.5); **4.5 Interaction with other medicinal products and other forms of interaction** Riociguat Serum concentrations may be increased due to CYP3A and P-gp inhibition by lopinavir/ritonavir. The co-administration of riociguat with Kaletra is not recommended (see section 4.4 and refer to riociguat SmPC).
UK	KALETRA (January, 2021)	**4.3 Contraindications** (No related description) **4.4 Special warnings and precautions for use**

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		Interactions with other medicinal products The combination of Kaletra with: - riociguat is not recommended (see section 4.5); **4.5 Interaction with other medicinal products and other forms of interaction** Riociguat Serum concentrations may be increased due to CYP3A and P-gp inhibition by lopinavir/ritonavir. The co-administration of riociguat with Kaletra is not recommended (see section 4.4 and refer to riociguat SmPC).
Canada	KALETRA (July, 2021)	(No related description)
Australia	KALETRA (July, 2020)	(No related description)

Table 3　Related description for concomitant use with riociguat in overseas package inserts of atazanavir sulfate

Country/region	Brand name (Version of package insert)	Description
US	REYATAZ (September, 2020)	(No related description)
EU	REYATAZ (February, 2022)	(No related description)
UK	REYATAZ* (January, 2021)	(No related description)
Canada	REYATAZ (April, 2020)	(No related description)
Australia	REYATAZ (December, 2021)	(No related description)

* The market authorization was withdrawn and the marketing was discontinued on December 31, 2021.

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Appendix 4

(Draft revision) Riociguat

Underlined: Revised language based on the investigation
Underlined with dotted lines: Revised language due to marketing discontinuation (completion of period of transitional measures)

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>
2. CONTRAINDICATIONS
2.7 Patients receiving azoles (itraconazole, voriconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir, indinavir, atazanavir, saquinavir), or ombitasvir/paritaprevir/ritonavir

10. INTERACTIONS
10.1 Contraindications for Co-administration
<table>
<tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>HIV protease inhibitors
Ritonavir (Norvir)
Lopinavir/ritonavir (Kaletra)</td><td>When co-administered with ketoconazole (oral dosage form, not marketed in Japan),</td><td>The clearance of riociguat is decreased by the inhibition of multiple CYP isoforms</td></tr>
</table>
</td><td>
2. CONTRAINDICATIONS
2.7 Patients receiving azoles (itraconazole, voriconazole)

10. INTERACTIONS
10.1 Contraindications for Co-administration
<table>
<tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>(deleted)</td><td>(deleted)</td><td>(deleted)</td></tr>
<tr><td>(deleted)</td><td>(deleted)</td><td>(deleted)</td></tr>
</table>
</td></tr>
</table>

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Indinavir (Crixivan) Atazanavir (Reyataz) Saquinavir (Invirase)	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 decreased.	(CYP1A1, CYP3A, etc.) and P-gp/BCRP.	
Ombitasvir/paritaprevir/ritonavir (Viekirax)	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	The clearance of riociguat is decreased by the inhibition of multiple CYP isoforms (CYP1A1, CYP3A, etc.) and P-gp/BCRP.	

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	addition, the elimination half-life was prolonged, and the clearance was decreased.	

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(N/A)	(N/A)	(N/A)

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Preparations containing ritonavir Atazanavir	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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		also be considered.		

N/A: Not Applicable. No corresponding language is included in the current Precautions.

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(Draft revision) Ritonavir

Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS 2.2 Patients receiving the following drugs: Quinidine sulfate hydrate, bepridil hydrochloride hydrate, flecainide acetate, propafenone hydrochloride, amiodarone hydrochloride, pimozide, piroxicam, ampiroxicam, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, eletriptan hydrobromide, vardenafil hydrochloride hydrate, sildenafil citrate (Revatio), tadalafil (Adcirca), azelnidipine, azelnidipine/olmesartan medoxomil, rifabutin, blonanserin, rivaroxaban, lomitapide mesilate, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], diazepam, clorazepate dipotassium, estazolam, flurazepam hydrochloride, triazolam, midazolam, lurasidone hydrochloride, riociguat, or voriconazole 10. INTERACTIONS	2. CONTRAINDICATIONS 2.2 Patients receiving the following drugs: Quinidine sulfate hydrate, bepridil hydrochloride hydrate, flecainide acetate, propafenone hydrochloride, amiodarone hydrochloride, pimozide, piroxicam, ampiroxicam, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, eletriptan hydrobromide, vardenafil hydrochloride hydrate, sildenafil citrate (Revatio), tadalafil (Adcirca), azelnidipine, azelnidipine/olmesartan medoxomil, rifabutin, blonanserin, rivaroxaban, lomitapide mesilate, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], diazepam, clorazepate dipotassium, estazolam, flurazepam hydrochloride, triazolam, midazolam, lurasidone hydrochloride, or voriconazole 10. INTERACTIONS

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10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Riociguat [Adempas]	It has been reported that the blood concentration of riociguat was increased and the clearance of riociguat was decreased when co-administered with ketoconazole.	The inhibitory activity of ritonavir against cytochrome P450 and transporters (P-gp, BCRP) may cause similar drug interactions.

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(N/A)	(N/A)	(N/A)

10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(deleted)	(deleted)	(deleted)

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Riociguat	The blood concentration of riociguat may increase. When co-administration with ritonavir is necessary,	The clearance of riociguat is decreased by the inhibition of CYP1A1 and CYP3A by ritonavir.

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		patients should be monitored for their conditions and dose reduction of riociguat should be considered as necessary.	

N/A: Not Applicable. No corresponding language is included in the current Precautions.

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(Draft revision) Lopinavir/ritonavir

Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>2. CONTRAINDICATIONS
2.2 Patients receiving the following drugs: Pimozide, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, midazolam, triazolam, lurasidone hydrochloride, vardenafil hydrochloride hydrate, sildenafil citrate (Revatio), tadalafil (Adcirca), blonanserin, azelnidipine, azelnidipine/olmesartan medoxomil, rivaroxaban, lomitapide mesilate, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], riociguat, voriconazole, or grazoprevir hydrate

10. INTERACTIONS
10.1 Contraindications for Co-administration</td><td>2. CONTRAINDICATIONS
2.2 Patients receiving the following drugs: Pimozide, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, midazolam, triazolam, lurasidone hydrochloride, vardenafil hydrochloride hydrate, sildenafil citrate (Revatio), tadalafil (Adcirca), blonanserin, azelnidipine, azelnidipine/olmesartan medoxomil, rivaroxaban, lomitapide mesilate, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], voriconazole, or grazoprevir hydrate

10. INTERACTIONS
10.1 Contraindications for Co-administration</td></tr>
<tr><td><table>
<tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>Riociguat</td><td>It has been reported</td><td>The inhibitory activity</td></tr>
</table></td><td><table>
<tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr>
<tr><td>(deleted)</td><td>(deleted)</td><td>(deleted)</td></tr>
</table></td></tr>
</table>

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[Adempas]	that the blood concentration of riociguat was increased and the clearance of riociguat was decreased when co-administered with ketoconazole.	of lopinavir/ritonavir against cytochrome P450 and that of ritonavir against transporters (P-gp, BCRP) may cause similar drug interactions.

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(N/A)	(N/A)	(N/A)

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Riociguat	The blood concentration of riociguat may increase. When co-administration with lopinavir/ritonavir is necessary, patients should be monitored for their conditions and	The clearance of riociguat is decreased by the inhibition of CYP1A1 and CYP3A by lopinavir/ritonavir.

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		dose reduction of riociguat should be considered as necessary.	

N/A: Not Applicable. No corresponding language is included in the current Precautions.

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(Draft revision) Atazanavir sulfate

Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision</th></tr>
<tr><td>2. CONTRAINDICATIONS
2.3 Patients receiving the following drugs: Rifampicin, irinotecan hydrochloride hydrate, midazolam, triazolam, bepridil hydrochloride hydrate, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, pimozide, simvastatin, lovastatin (not marketed in Japan), lomitapide mesilate, vardenafil hydrochloride hydrate, blonanserin, azelnidipine, olmesartan medoxomil/azelnidipine, lurasidone hydrochloride, rivaroxaban, riociguat, grazoprevir hydrate, glecaprevir hydrate/pibrentasvir, proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, esomeprazole, vonoprazan fumarate), aspirin/lansoprazole, aspirin/vonoprazan fumarate, or St. John's Wort

10. INTERACTIONS
10.1 Contraindications for Co-administration</td><td>2. CONTRAINDICATIONS
2.3 Patients receiving the following drugs: Rifampicin, irinotecan hydrochloride hydrate, midazolam, triazolam, bepridil hydrochloride hydrate, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, pimozide, simvastatin, lovastatin (not marketed in Japan), lomitapide mesilate, vardenafil hydrochloride hydrate, blonanserin, azelnidipine, olmesartan medoxomil/azelnidipine, lurasidone hydrochloride, rivaroxaban, grazoprevir hydrate, glecaprevir hydrate/pibrentasvir, proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, esomeprazole, vonoprazan fumarate), aspirin/lansoprazole, aspirin/vonoprazan fumarate, or St. John's Wort

10. INTERACTIONS
10.1 Contraindications for Co-administration</td></tr>
<tr><td><table><tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr></table></td><td><table><tr><th>Drugs</th><th>Signs, Symptoms, and Treatment</th><th>Mechanism and Risk Factors</th></tr></table></td></tr>
</table>

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Riociguat (Adempas)	It has been reported that the blood concentration of riociguat was increased and the clearance of riociguat was decreased when co-administered with ketoconazole.	The clearance of riociguat is decreased by the inhibition of multiple CYP isoforms (CYP1A1, CYP3A, etc.) and P-gp/breast cancer resistance protein (BCRP).

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(N/A)	(N/A)	(N/A)

(deleted)	(deleted)	(deleted)

10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Riociguat	The blood concentration of riociguat may increase. When co-administration with atazanavir sulfate is necessary, patients should be monitored for their conditions and	The clearance of riociguat is decreased by the inhibition of CYP3A4 by atazanavir sulfate.

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		dose reduction of riociguat should be considered as necessary.	

N/A: Not Applicable. No corresponding language is included in the current Precautions.