Pharmaceuticals and Medical Devices Safety Information

No. 395

Table of Contents

This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (https://www.pmda.go.jp/english/) and on the MHLW website (https://www.mhlw.go.jp/, only available in Japanese language).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

Register here

Published by
Ministry of Health, Labour and Welfare

Pharmaceutical Safety and Environmental Health Bureau, Labour and Welfare,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

This English version of PMDSI 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. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 395

Ministry of Health, Labour and Welfare
Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)
https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse Drug Reaction
BCRP	Breast Cancer Resistance Protein
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HIV	Human Immunodeficiency Virus
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
TMA	Thrombotic Microangiopathy

1
Revision of Precautions regarding the Co-administration of Riociguat with HIV Protease Inhibitors

1. Introduction

Riociguat is approved for marketing in Japan for the indications of the treatment of “inoperable chronic thromboembolic pulmonary hypertension (hereinafter referred to as “CTEPH”) or postoperative persistent or recurrent CTEPH, and pulmonary arterial hypertension,” and co-administration of riociguat with human immunodeficiency virus (hereinafter referred to as “HIV”) protease inhibitors (ritonavir, lopinavir/ritonavir, atazanavir sulfate) was contraindicated.

Recently, CONTRAINDICATIONS and Contraindications for Co-administrations of riociguat and HIV protease inhibitors were revised based on the deliberation in the 10th fiscal year (FY) 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as “the Subcommittee on Drug Safety”) held on August 30, 2022. This section will introduce the details of the revision.

2. Background

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 resistance protein (hereinafter referred to as “BCRP”). In the drug-drug interaction study of riociguat with ketoconazole, which is an inhibitor of multiple CYP isoforms, P-gp, and BCRP, the exposure of riociguat after concomitant use with ketoconazole was increased compared to that after administration of riociguat alone. Therefore, 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. Thus, concomitant use of HIV protease inhibitors with riociguat was specified in CONTRAINDICATIONS and Contraindications for Co-administration.

Recently, the results of clinical trials investigating the pharmacokinetic drug-drug interactions between riociguat and anti-HIV drugs including HIV protease inhibitors (hereinafter referred to as “drug-drug interaction study”) 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 of riociguat.

Taking into account the above mentioned, the Subcommittee on Drug Safety discussed the revision of CONTRAINDICATIONS and Contraindications for Co-administration, etc.

3. Deliberation by the Subcommittee on Drug Safety

As a result of investigating the results of the drug-drug interaction study, the *in vitro* studies, etc., adverse event case reports, pertinent published literature, statements in Japanese and overseas clinical practice guidelines, and current descriptions of overseas package inserts, PMDA concluded that contraindications for co-administrations of riociguat with HIV protease inhibitors may be lifted and that these may be specified in Precautions for Co-administration for the following points.

- The exposure of riociguat was increased by approximately 1.3-fold when it was co-administered with HIV protease inhibitors compared to that of riociguat administered alone. Considering that riociguat is a drug that is started at a low dose and titrated according to the patient's condition, it should be possible to ensure a margin of safety by starting riociguat at a lower dose than the usual starting dose.
- In the overseas package inserts, concomitant use of riociguat with HIV protease inhibitors is not

contraindicated. Adverse event reports and published literature, etc. did not identify any particular clinical concerns.
- In the drug-drug interaction study of riociguat and anti-HIV drugs, no particular safety problems were observed when riociguat was co-administered with anti-HIV drugs.

However, it was decided that the following precaution should be provided: Starting riociguat at a lower dose (0.5 mg of riociguat 3 times a day) than the usual starting dose or reducing the dose as necessary should be considered when riociguat and anti-HIV drugs are co-administered.

4. Closing remark

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the electronic package inserts for a careful decision on the co-administration of riociguat with HIV protease inhibitors. Continued cooperation by healthcare professionals for proper use of this drug would be appreciated.

[References]
Materials 1-1 to 1-3 of the 10th FY 2022 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on August 30, 2022)
https://www.mhlw.go.jp/stf/newpage_27607.html (only in Japanese)
Revision of Precautions (PSEHB/PSD Notification No. 0913-6 dated September 13, 2022)
https://www.pmda.go.jp/files/000248127.pdf (in Japanese)
English translation by PMDA (September 13, 2022)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated August 30, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Ramucirumab (genetical recombination)

Brand name (name of company)	Cyramza Intravenous Injection 100 mg, 500 mg (Eli Lilly Japan K.K.)
Therapeutic category	Other antitumor agents
Indications	·Incurable, unresectable, advanced or recurrent gastric cancer ·Incurable, unresectable, advanced or recurrent colorectal cancer ·Unresectable advanced or recurrent non-small cell lung cancer ·Unresectable hepatocellular carcinoma with serum AFP greater than 400 ng/mL that has progressed after chemotherapy

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS	Thrombotic microangiopathy
11.1 Clinically Significant Adverse Reactions (newly added)	If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period Cases involving thrombotic microangiopathy: 6 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 77 400 Japanese market launch: June 2015

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 70s	Colorectal cancer (none)	300 mg (2 courses at 2-week intervals)	**Thrombotic microangiopathy** Approximately 5 months before administration: The patient received mFOLFOX6 therapy+ bevacizumab (12 courses) as the first line treatment for colorectal cancer. Day 1 of administration: FOLFIRI therapy + administration of ramucirumab 300 mg was initiated as the second line treatment. Red blood cell (RBC): 3 990 000/μL, hemoglobin (Hb): 11.6 g/dL, platelet (Plt): 124 000/μL 14 days after administration: The patient received FOLFIRI therapy + the second dose of ramucirumab. RBC: 3 720 000/μL, Hb: 10.9 g/dL, Plt: 113 000/μL, urinary protein: 1+ 28 days after administration: Urinary protein: 4+ The patient had oedema. Decreased platelets were also observed, FOLFIRI

			(day of discontinuation)	therapy was postponed, and administration of ramucirumab was discontinued. RBC: 3 550 000/μL, Hb: 10.5 g/dL, Plt: 37 000/μL, urinary protein: 4+
			7 days after discontinuation	Urinary protein exceeded 3 g/day. RBC: 3 470 000/μL, Hb: 10.3 g/dL, Plt: 75 000/μL
			14 days after discontinuation	FOLFIRI therapy was postponed due to high urinary protein. RBC: 3 550 000/μL, Hb: 10.6 g/dL, Plt: 83 000/μL, urinary protein: 4+
			21 days after discontinuation	The patient was diagnosed with thrombotic microangiopathy (TMA) according to renal disorder and symptoms by the nephrologist. She was followed up with suspension of FOLFIRI therapy. Renal biopsy: Not performed RBC: 3 630 000/μL, Hb: 10.7 g/dL, Plt: 81 000/μL, urinary protein: 4+, schizocytes: 0.2%
			28 days after discontinuation	RBC: 3 530 000/μL, Hb: 10.5 g/dL, Plt: 153 000/μL, urinary protein: 2+
			42 days after discontinuation	TMA was resolving. FOLFIRI therapy was resumed. RBC: 3 930 000/μL, Hb: 11.6 g/dL, Plt: 191 000/μL, urinary protein: 1+

Laboratory test value

	Day 1 of admin.	14 days after admin.	28 days after admin.	7 days after discontinuation	14 days after discontinuation	21 days after discontinuation	28 days after discontinuation	42 days after discontinuation
RBC (/μL)	3 990 000	3 720 000	3 550 000	3 470 000	3 550 000	3 630 000	3 530 000	3 930 000
Hb (g/dL)	11.6	10.9	10.5	10.3	10.6	10.7	10.5	11.6
Plt (/μL)	124 000	113 000	37 000	75 000	83 000	81 000	153 000	191 000
LDH (/μL)	265	233	379	407	435	455	325	250
BUN (mg/dL)	15	16	23	20	15	18	12	17
CRE (mg/dL)	0.56	0.60	0.67	0.82	0.77	0.77	0.65	0.62
Urine micro-albumin (mg/gCr)	—	—	—	3629.5	7106.4	7746.9	6556.7	2626.5
Urinary protein	—	(1+)	(4+)	—	(4+)	(4+)	(2+)	(1+)
PT (seconds)	—	—	—	—	—	9.9	10.0	10.4
APTT (seconds)	—	—	—	—	—	33.5	30.6	30.5
FIB (mg/dL)	—	—	—	—	—	468	477	448
D-dimer (μg/mL)	—	—	—	—	—	2.35	1.59	0.89
Schizocytes (%)	—	—	—	—	—	0.2	—	—

Concomitant drugs: Fluorouracil, levofolinate, irinotecan

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 40s	Cancer of sigmoid colon (metastases to liver, metastases to bone, metastases to lung, metastases to lymph nodes)	430 mg (2 courses at 2-week intervals)	**Thrombotic microangiopathy**	
				Approx. 9 months before administration	FOLFOX therapy was initiated for cancer of sigmoid colon.
				Approx. 1 month before administration	FOLFOXIRI therapy was initiated for cancer of sigmoid colon.
				30 days before administration	RBC: 4 060 000/μL, Hb: 12.4 g/dL, Plt: 154 000/μL
				Day 1 of administration	FOLFIRI therapy + administration of ramucirumab was initiated for cancer of sigmoid colon. (adenocarcinoma, T4aN3M1) RBC: 3 880 000/μL, Hb: 11.8 g/dL, Plt: 152 000/μL
				A few days after administration	Edema, increased blood pressure (BP), and tendency to gain weight were noted.
				14 days after administration	The patient received FOLFIRI therapy + ramucirumab (final administration).
				28 days after administration (Day of discontinuation)	FOLFIRI therapy + administration of ramucirumab was postponed due to Alb value of 3.2 g/dL. RBC: 4 010 000/μL, Hb: 11.8 g/dL, Plt: 80 000/μL, eGFR: 53 mL/min/1.73m^2, urinary protein: 4+
				14 days after discontinuation	Nephrotic syndrome was suspected, and the patient visited the nephrology department. RBC: 4 440 000/μL, Hb: 13.0 g/dL, Plt: 123 000/μL, eGFR: 53 mL/min/1.73 m^2, urinary protein: 4+
				15 days after discontinuation	The patient was diagnosed with nephrotic syndrome. She was admitted to the hospital for scrutiny and treatment. Salt intake was restricted. Treatment was initiated with furosemide, amlodipine, and candesartan. Hb: 13.5 g/dL No schistocytes were observed. There were no findings suggesting secondary nephritis in blood and urine tests. RBC: 4 580 000/μL, Hb: 13.5 g/dL, Plt: 120 000/μL, eGFR: 55 mL/min/1.73 m^2, urinary protein: 4+
				18 days after discontinuation	Haptoglobin: ≤10 mg/dL
				20 days after discontinuation	Primary nephritis or nephrotic syndrome by ramucirumab was suspected, and a renal biopsy was performed. [Light microscopic findings] Focal segmental enlargement of the mesangial area, infiltration of foam cells in the tuft, and deposits stained reddish-purple by Masson staining in the mesangial area under the endothelium were noted. In addition, numerous double contours of glomerular basement membrane were observed. The stroma was slightly edematous, with partial fibrosis and cellular infiltration. Vacuolar degeneration of the

				tubular epithelium was observed in some places. [Fluoroscopic findings] IgM, C4 showed luminescence in a fringe pattern consistent with the glomerular basement membrane. [Pathological tissue] Chronic proliferative glomerulonephritis-like lesions were present, consistent with TMA-like lesions. Based on the above, the patient was diagnosed with drug-induced nephrotic syndrome caused by ramucirumab. RBC: 3 780 000/μL, Hb: 11.1 g/dL, Plt: 99 000/μL, eGFR: 66 mL/min/1.73 m^2, urinary protein: 2+
			22 days after discontinuation	Haptoglobin: 61 mg/dL
			28 days after discontinuation	Urinary protein was resolving due to discontinuation of ramucirumab and administration of candesartan. The patient was discharged from the hospital. RBC: 3 780 000/μL, Hb: 11.2 g/dL, Plt: 171 000/μL, eGFR: 75 mL/min/1.73m^2, urinary protein: 2+
			70 days after discontinuation	Complete remission was obtained for drug-induced nephrotic syndrome. RBC: 3 690 000/μL, Hb: 11.0 g/dL, Plt: 225 000/μL, eGFR: 76 mL/min/1.73m^2, urinary protein: 1+

Laboratory test value

	31 days before administration	30 days before administration	Day 1 of administration	14 days after administration	28 days after administration	42 days after administration
RBC (/μL)	-	4 060 000	3 880 000	-	4 010 000	4 440 000
Hb (g/dL)	-	12.4	11.8	-	11.8	13.0
Plt (/μL)	-	154 000	152 000	-	80 000	123 000
LDH (U/L)	-	-	-	-	317	370
Albumin (g/dL)	-	-	-	-	3.2	2.4
BUN (mg/dL)	-	-	-	-	12.5	19.8
CRE (mg/dL)	-	-	-	-	0.92	0.92
eGFR (mL/min/1.73 m^2)	-	-	-	-	53	53
CRP (mg/dL)	-	-	-	-	0.08	0.07
Urinary protein	-	-	-	-	4+	4+
PT time (seconds)	10.3	-	-	10.3	-	-
PT activity (%)	≥130	-	-	≥130	-	-
PT-INR	1.00>	-	-	1.00>	-	-
APTT (seconds)	30.5	-	-	30.4	-	-
FIB (mg/dL)	348	-	-	246	-	-
FDP (ug/mL)	-	-	-	-	-	-
D-dimer (μg/mL)	-	-	-	-	-	-
Urine protein /Cr ratio (g/gCr)	-	-	-	-	0.69	9.32
IgG (mg/dL)	-	-	-	-	-	-
IgA (mg/dL)	-	-	-	-	-	-

IgM (mg/dL)	-	-	-	-	-	-
Complement Component C3 (mg/dL)	-	-	-	-	-	-
Complement Component C4 (mg/dL)	-	-	-	-	-	-
Haptoglobin (mg/dL)	-	-	-	-	-	-

	43 days after administration	46 days after administration	48 days before administration	50 days after administration	56 days after administration	98 days after administration
RBC (/μL)	4 580 000	-	3 780 000	-	3 780 000	3 690 000
Hb (g/dL)	13.5	-	11.1	-	11.2	11.0
Plt (/μL)	120 000	-	99 000	-	171 000	225 000
LDH (U/L)	386	-	290	-	426	317
Albumin	2.5	-	1.9	-	2.5	3.5
BUN (mg/dL)	17.3	-	9.0	-	10.2	10.1
CRE (mg/dL)	0.89	-	0.75	-	0.67	0.66
eGFR (ml/min/1.73 m2)	55	-	66	-	75	76
CRP (mg/dL)	0.06	-	0.06	-		0.17
Urinary protein	4+	-	2+	-	2+	1+
PT time (seconds)	9.7	-	-	-	-	-
PT activity (%)	≧130	-	-	-	-	-
PT-INR	1.00>	-	-	-	-	-
APTT (seconds)	29.6	42.7	-	-	-	-
FIB (mg/dL)	480	417	-	-	-	-
FDP (ug/mL)	8.70	-	-	-	-	-
D-dimer (ug/mL)	2.87	2.39	-	-	-	-
Urine protein/Cr ratio (g/gCr)	8.22	-	-	-	1.17	0.28
IgG (mg/dL)	339	-	-	-	-	-
IgA (mg/dL)	159	-	-	-	-	-
IgM (mg/dL)	166	-	-	-	-	-
Complement Component C3 (mg/dL)	140	-	-	-	-	-
Complement Component C4 (mg/dL)	23	-	-	-	-	-
Haptoglobin (mg/dL)	-	10	-	61	-	-

Concomitant drugs: Fluorouracil, levofolinate, irinotecan

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
3	Female 70s	Rectal cancer (multiple metastases in the residual lower lobe of the right lung)	300 mg (1 course)	**Thrombotic microangiopathy** Medical history: Hepatitis B, hypertension Approximately 14 years and 5 months before administration: The patient was diagnosed with rectal cancer (Rs, T3 (SS) N1M0, pStageIIIa, R0, pCurA). Approximately 6 years and 10 months before administration: The patient was treated with XELOX therapy for metastatic lung cancer (2 courses). Thereafter, capecitabine was administered as the sole regimen. Approximately 2 years and 7 months before administration: mFOLFOX6 therapy + administration of bevacizumab was initiated. Thereafter, treatment with fluorouracil + levofolinate + bevacizumab was conducted (22 courses in total). Approximately 1 month before administration: Pulmonary metastasis was enlarged. 1 day before administration: RBC: 4 280 000/μL, Hb: 12.3 g/dL, Plt: 241 000/μL, eGFR: 58.8 mL/min, urinary protein: +- Day 1 of administration: FOLFIRI therapy + administration of ramucirumab 300 mg was initiated for recurrent rectal cancer (the last day of administration of ramucirumab). Thereafter, the patient had grade 1 inappetence, tired feeling, and symptoms of diarrhoea. 16 days after administration: The patient noticed lower leg oedema. At that time, she had voice alteration and difficulty breathing. Between Day 16 and 24 of administration: BP: 165/90 mmHg, HR: 102/min The patient gained 7 kg, weighing 50.2 kg. 24 days after administration: Severe oedema and urinary protein were observed, and the patient was diagnosed with suspected nephrotic syndrome. She was immediately admitted to the hospital for detailed examination of the cause. Administration of furosemide 40 mg and azosemide 60 mg was initiated. RBC: 4 010 000/μL, Hb: 11.1 g/dL, Plt: 95 000/μL, eGFR: 38.0 mL/min, urinary protein: 4+, schizocytes: 3%, BP: 141/88 mmHg, body weight: 49.8 kg 27 days after administration: RBC: 3 740 000/μL, Hb: 10.6 g/dL, Plt: 77 000/μL, eGFR: 36.8 mL/min, urinary protein: 4+ 29 days after administration: Drug-induced nephrotic syndrome was suspected, and the patient underwent renal biopsy. At the time of the procedure, azosemide 60 mg and atorvastatin calcium hydrate 10 mg were administered. Renal biopsy, findings in the fluorescent antibody method: IgA: ±, IgG: ±, IgM: +, Fib: +-, C3: -, C4: 1+, C1q: ±. Renal biopsy, histological findings: Ratio of cortex versus medulla was 9 to 1. Total number of glomeruli: 16 Blood clots giving positive fibrin staining were confirmed in the glomerular tuft. Tumefied endothelial cells in glomerular tufts, increase in mesangial matrix, double contours of glomerular basement membrane were observed, and the change in the tubulointerstitium was mild. (Local infiltration of lymphoid cell was noted.) Hyperplasia of endarterium accompanying fibrin

					precipitation was observed under the vascular endothelium. Hb: 11.1 g/dL, Plt: 95 000/μL, eGFR: 39.7 mL/min, urinary protein: 4+, haptoglobin: <10, schizocytes: 5%, BP: 141/81 mmHg, body weight: 47.9 kg
				30 days after administration	Administration of spironolactone 25 mg was initiated. RBC: 3 680 000/ μL, Hb: 10.7 g/dL, Plt: 80 000/μL, eGFR: 36.8 mL/min, urinary protein: 4+, BP: 155/83 mmHg, body weight: 46.8 kg
				31 days after administration	Administration of telmisartan 20 mg was initiated.
				34 days after administration	RBC: 3 470 000/μL, Hb: 10.0 g/dL, Plt: 124 000/μL, eGFR: 45.1 mL/min
				37 days after administration	The results of renal biopsy, which was performed 29 days after administration, did not contradict the finding of thrombotic microangiopathy (TMA). The patient was diagnosed with drug-induced TMA associated with administration of ramucirumab and drug-induced nephrotic syndrome due to TMA. Conservative treatment with renin-angiotensin inhibitor was taken. RBC: 3 490 000/μL, Hb: 9.8 g/dL, Plt: 196 000/μL, eGFR: 47.0 mL/min, urinary protein: 3+, BP: 166/82 mmHg, body weight: 42.5 kg
				38 days after administration	The patient recovered from drug-induced nephrotic syndrome.
				39 days after administration	Administration of increased dose of telmisartan 40 mg was initiated. The patient was discharged from the hospital.
				51 days after administration	RBC: 4 140 000/μL, Hb: 11.6 g/dL, Plt: 304 000/μL, eGFR: 33.0 mL/min, urinary protein: 1+
				79 days after administration	The patient recovered from drug-induced TMA.

Laboratory test value

	1 day before admin.	24 days after admin.	27 days after admin.	29 days after admin.	30 days after admin.
RBC (/μL)	4 280 000	4 010 000	3 740 000	-	3 680 000
Hb (g/dL)	12.3	11.1	10.6	11.1	10.7
Plt (/μL)	241 000	95 000	77 000	95 000	80 000
LDH (/μL)	164	295	277	-	317
Total protein (g/dL)	6.6	5.1	4.3	5.1	-
Albumin (g/dL)	4.3	3.2	2.6	3.2	2.7
BUN (mg/dL)	13	14	12	14	14
CRE (mg/dL)	0.57	0.84	0.92	0.84	0.90
eGFR (mL/min)	58.8	38.0	36.8	39.7	36.8
Urinary protein	+-	4+	4+	4+	4+
Urinary occult blood	-	3+	2+	3+	2+
WBC response (/μL)	0 (-)	25 (+-)	0 (-)	-	0 (-)
PT-INR	0.92	0.88	0.93	-	-
Schizocytes	-	3%	-	5%	-
Urine protein/creatinine ratio (g/gCr)	-	-	-	11.06	-
IgG (mg/dL)	-	-	-	407	-
IgA (mg/dL)	-	-	-	138	-
IgM (mg/dL)	-	-	-	58	-
C3 (mg/dL)	-	-	-	105	-

C4 (mg/dL)	-	-	-	16	-
Urinary WBC casts	-	-	-	Positive	-
Urinary β_2 -microglobulin (μg/L)	-	-	-	1379	-
Haptoglobin	-	-	-	<10	-
ADAMTS13 activity	-	-	-	61.8%	-
ADAMTS13 inhibitor	-	-	-	Negative	-
PR3-ANCA (EU)	-	-	-	<1.0	-
MPO-ANCA (E)(EU)	-	-	-	<1.0	-

	34 days after admin.	37 days after admin.	51 days after admin.
RBC (/μL)	3 470 000	3 490 000	4 140 000
Hb (g/dL)	10.0	9.8	11.6
Plt (/μL)	124 000	196 000	304 000
LDH (/μL)	296	269	194
Total protein (g/dL)	4.5	4.6	6.2
Albumin (g/dL)	2.7	2.7	3.5
BUN (mg/dL)	7	8	15
CRE (mg/dL)	0.74	0.69	0.94
eGFR (mL/min)	45.1	47.0	33.0
Urinary protein	-	3+	1+
Urinary occult blood	-	1+	1+
WBC response (/μL)	-	0 (-)	75 (1+)
PT-INR	0.91	-	0.90
Schizocytes	-	-	-
Urine protein/creatinine ratio (g/gCr)	-	-	-
IgG (mg/dL)	-	-	-
IgA (mg/dL)	-	-	-
IgM (mg/dL)	-	-	-
C3 (mg/dL)	-	-	-
C4 (mg/dL)	-	-	-
Urinary WBC casts	-	-	-
Urinary β_2 -microglobulin (μg/L)	-	-	-
Haptoglobin	-	-	-
ADAMTS13 activity	-	-	-
ADAMTS13 inhibitor	-	-	-
PR3-ANCA (EU)	-	-	-
MPO-ANCA (E)(EU)	-	-	-

Concomitant drugs: Fluorouracil, levofolinate, irinotecan

3
Revision of Precautions (No.335)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated August 30, September 13, 2022.

1 Agents affecting metabolism, n.e.c. (not elsewhere classified)
Hydroxychloroquine sulfate

Brand name
[Under New instructions]
Plaquenil Tablets 200 mg (Sanofi K.K.)

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Hepatic impairment
Hepatic impairment accompanied by increased levels of AST, ALT and γ-GTP, etc. may occur.

2 Other antitumor agents
Ramucirumab (genetical recombination)

Brand name
[Under New instructions]
Cyramza Intravenous Injection 100 mg, 500 mg (Eli Lilly Japan K.K.)

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Thrombotic microangiopathy
If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

3 Other cardiovascular agents
Riociguat

Brand name
[Under New instructions]
Adempas tablets 0.5 mg, 1.0 mg, 2.5 mg (Bayer Yakuhin, Ltd.)

2. CONTRAINDICATIONS

Patients receiving azoles (itraconazole, voriconazole), HIV protease inhibitors (indinavir, saquinavir), or ombitasvir/paritaprevir/ritonavir

10. INTERACTIONS
10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
HIV protease inhibitors (indinavir, saquinavir)	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 decreased.	The clearance of riociguat is decreased by the inhibition of multiple CYP isoforms (CYP1A1, CYP3A, etc.) and P-gp/BCRP.

10.2 Precautions for Co-administration (newly added)

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 also be considered.	The clearance of riociguat is decreased by the inhibition of CYP1A1 and/or CYP3A by these drugs.

4 Anti-virus agents

Atazanavir sulfate

Brand name
[Under New instructions]
Reyataz Capsules 150 mg, 200 mg (Bristol-Myers Squibb K.K.)

2. CONTRAINDICATIONS
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
(deleted)

10.2 Precautions for Co-administration (newly added)

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 dose reduction of riociguat should be considered as necessary.	The clearance of riociguat is decreased by the inhibition of CYP3A4 by atazanavir sulfate.

5 Anti-virus agents

Ritonavir

Brand name
[Under New instructions]
Norvir Tablets 100 mg (AbbVie GK)

2. CONTRAINDICATIONS

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
10.1 Contraindications for Co-administration
10.2 Precautions for Co-administration (newly added)

(deleted)

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

6 Anti-virus agents

Lopinavir/ritonavir

Brand name

Kaletra Combination Tablets, Kaletra Combination Oral Solution (AbbVie GK)

[Under New instructions]

2. CONTRAINDICATIONS

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
10.2 Precautions for Co-administration (newly added)

(deleted)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Riociguat	The blood concentration of	The clearance of riociguat is decreased

		riociguat may increase. When co-administration with lopinavir/ritonavir is necessary, patients should be monitored for their conditions and dose reduction of riociguat should be considered as necessary.	by the inhibition of CYP1A1 and CYP3A by lopinavir/ritonavir.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of July 31, 2022)
◎: Products for which EPPV was initiated after July 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
	[1] [2] Cabotegravir, [3] Cabotegravir sodium, [4] [5] Rilpivirine [1] Vocabria Aqueous Suspension for IM Injection 400 mg, [2] Vocabria Aqueous Suspension for IM Injection 600 mg, [3] Vocabria Tablets 30 mg, [4] Rekambys Aqueous Suspension for IM Injection 600 mg, [5] Rekambys Aqueous Suspension for IM Injection 900 mg	[1] [2] [3] ViiV Healthcare K.K. [1] [2] Janssen Pharmaceutical K.K.	June 27, 2022
	Emicizumab (genetical recombination)*1 Hemlibra for Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	June 20, 2022
	Daptomycin Cubicin IV 350 mg	MSD K.K.	June 20, 2022
	Brolucizumab (genetical recombination) *2 Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	June 20, 2022
	Rituximab (genetical recombination) *3 Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	June 20, 2022
	Lasmiditan succinate Reyvow tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	June 8, 2022
	Avacopan Tavneos Capsules 10 mg	Kissei Pharmaceutical Co., Ltd.	June 7, 2022
	Olipudase alfa (genetical recombination) Xenpozyme for I.V. Infusion 20 mg	Sanofi K.K.	June 3, 2022
	Finerenone Kerendia tablets 10 mg, 20 mg	Bayer Yakuhin Ltd.	June 2, 2022
	Valbenazine tosilate Dysval Capsules 40 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2022
	Difamilast Moizerto ointment 0.3%, 1%	Otsuka Pharmaceutical Co., Ltd.	June 1, 2022
	Carotegrast methyl	EA Pharma Co., Ltd.	May 30,

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Carogra Tablets 120 mg		2022
Fosnetupitant chloride hydrochloride Arokaris I.V. infusion 235 mg	TAIHO Pharmaceutical Co., Ltd.	May 30, 2022
Tolvaptan sodium phosphate Samtasu for I.V. infusion 8 mg, 16 mg	Otsuka Pharmaceutical Co., Ltd.	May 30, 2022
Lanadelumab (genetical recombination) Takhzyro subcutaneous injection 300 mg syringes	Takeda Pharmaceutical Company Limited.	May 30, 2022
Metronidazole[*4] Rozex Gel 0.75%	Maruho Co., Ltd.	May 26, 2022
Asciminib hydrochloride Scemblix tablets 20 mg, 40 mg	Novartis Pharma K.K.	May 25, 2022
Faricimab (genetical recombination) Vabysmo solution for Intravitreal Injection 120 mg/mL	Chugai Pharmaceutical Co., Ltd.	May 25, 2022
Andexanet alfa (genetical recombination) Ondexxya for Intravenous Injection 200 mg	Alexion Pharma Godo Kaisha	May 25, 2022
Glycopyrronium tosilate hydrate Rapifort Wipes 2.5%	Maruho Co., Ltd.	May 23, 2022
Recombinant COVID-19 (SARS-CoV-2) vaccine Nuvaxovid Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 10, 2022
Efgartigimod Alfa (genetical recombination) Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	May 9, 2022
Somatrogon (genetical recombination) Ngenla Inj. 24 mg Pens, 60 mg Pens	Pfizer Japan Inc.	April 27, 2022
Gefapixant citrate Lyfnua Tablets 45 mg	MSD K.K.	April 21, 2022
Sotorasib Lumakras Tablets 120 mg	Amgen K.K.	April 20, 2022
Clazosentan sodium Pivlaz I.V. Infusion liquid 150 mg	Idorsia Pharmaceuticals Japan Ltd.	April 20, 2022
Bimekizumab (genetical recombination) Bimzelx Syringe for S.C injection 160 mg, Bimzelx Autoinjector for S.C injection 160 mg	UCB Japan Co. Ltd.	April 20, 2022
Filgotinib maleate[*5] Jyseleca Tablets 100 mg, 200 mg	Gilead Sciences K.K.	March 28, 2022
Selpercatinib[*6] Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	February 25, 2022
Pegfilgrastim (genetical recombination)[*7] G-Lasta Subcutaneous Injection 3.6 mg	Kyowa Kirin Co., Ltd.	February 25, 2022
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 5 to 11 years old	Pfizer Japan Inc.	February 22, 2022
Nirmatrelvir/ritonavir	Pfizer Japan Inc.	February 14,

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	Paxlovid Pack		2022

*1 Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with acquired hemophilia A

*2 Diabetic macular oedema

*3 Prevention of recurrence of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

*4 Rosacea

*5 Treatment and maintenance therapy for moderately to severely active ulcerative colitis (limited to patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapies)

*6 Radically unresectable RET fusion-positive thyroid cancer, radically unresectable RET-mutant medullary thyroid cancer

*7 Mobilization of haematopoietic stem cells into peripheral blood for allogeneic blood stem cell transplantation