Pharmaceuticals and Medical Devices Safety Information

No. 411 July 2024

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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) web page (https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html) and on the MHLW website (https://www.mhlw.go.jp/, only in Japanese).

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 the MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.
This service is available only in Japanese.

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No. 411 July 2024

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

[Outline of Information]

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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 healthcare professionals.

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

Please utilize the Report Reception Site for reporting.
(This service is available only in Japanese.)

https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse Drug Reaction
DPC	Diagnosis Procedure Combination
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MID-NET	Medical Information Database NETwork
OCT	Optical Coherence Tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division

1

Revisions of PRECAUTIONS for Preparations Containing Brimonidine Tartrate

1. Introduction

Brimonidine tartrate, brimonidine tartrate/timolol maleate, brimonidine tartrate/brinzolamide, and ripasudil hydrochloride hydrate/brimonidine tartrate (hereinafter referred to as “preparations containing brimonidine tartrate”) are used for the treatment of glaucoma and ocular hypertension in patients who have not responded sufficiently to other anti-glaucoma drugs.

As a result of the investigation including the opinions of expert advisors regarding the possible occurrence of serious corneal opacity in patients receiving preparations containing brimonidine tartrate, the MHLW considered it necessary to take safety measures, and issued a notification instructing the marketing authorization holders (MAHs) to revise PRECAUTIONS on June 11, 2024. This section will introduce the details of the revision and other relevant information.

2. Background

Precautions for corneal opacity have been added to the "Other Adverse Reactions" section of the electronic package insert for brimonidine tartrate since 2019 and for other preparations containing brimonidine tartrate since their approval. Recently, the MAH of the preparations containing brimonidine tartrate requested a consultation with the PMDA concerning revision of the package insert to add the risk of serious corneal opacity in the IMPORTANT PRECAUTIONS and Clinically Significant Adverse Reactions sections in order to alert healthcare professionals based on the cases reported after marketing involving serious corneal opacity and literature information, and then the necessity of revision of the electronic package insert was deliberated.

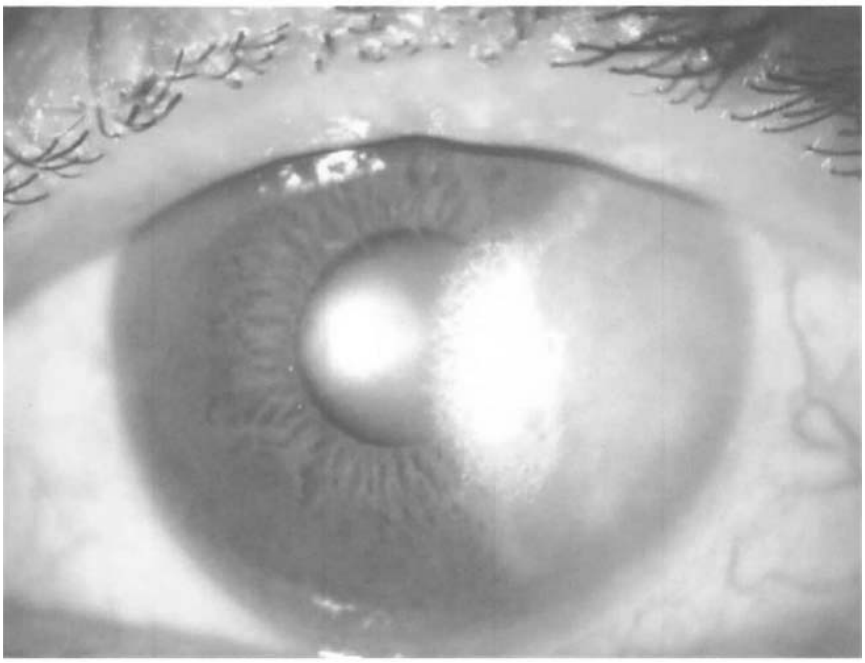
3. Details of the review

It was assumed that corneal opacity developed due to an inflammatory response induced after administration of preparations containing brimonidine tartrate.[1)] Among the cases reported in Japan* which fell under “corneal opacity” or “corneal infiltrates,” cases with a best-corrected visual acuity of lower than 0.5, cases with lesions (e. g., opacity, interstitial keratitis, neovascularisation, and steatosis) in the pupillary area, or cases in which corneal transplant surgery, etc. had been performed were retrieved. Among those 19 retrieved cases, 11 reported cases for which a causal relationship between the preparations containing brimonidine tartrate and event was reasonably possible have been confirmed.

In addition, among cases of serious corneal opacity, especially for the cases in which corneal opacity spread from the peripheral part of the cornea to the central part in a fan-like pattern developing into the central part of the cornea (pupillary area) (Figure 1 below), it is known that the opacity part becomes scarred even after discontinuation of the preparations, resulting in poor visual prognosis.[2)] Special attention should be paid to these cases. If corneal infiltration or corneal neovascularisation is observed as a prodromal symptom, it is important to discontinue administration of the preparations and to administer steroid eye drops at that time. Therefore, ophthalmologists must monitor the presence or absence of findings such as corneal infiltration or corneal neovascularisation through periodic medical examinations. If any findings of prodromal symptoms or corneal opacity are observed, ophthalmologists are encouraged to take appropriate measures.

* Cases collected in the PMDA's database for adverse drug reactions, etc. reports

Figure (1): A case in which corneal opacity spread from the peripheral part of the cornea to the central part in a fan-like pattern developing into the central part of the cornea (pupillary area)



Glaucoma and ocular hypertension are diseases that require periodic visits to the ophthalmologists for many patients. However, based on the fact that those diseases suddenly occurred and progressed in some reported cases of serious corneal opacities, and considering the points for early detection, etc. described in the Manuals for Management of Individual Serious Adverse Drug Reactions for corneal opacity issued by the MHLW, ophthalmologists are requested to explain to patients that they should immediately consult their ophthalmologists without waiting for the next consultation day if any subjective symptoms including hyperaemia, reduced visual acuity, or blurred vision occur.

4. Closing comments

Healthcare professionals are requested to understand the purpose of the revision this time and to carefully check the electronic package inserts for a careful decision. Continued cooperation by healthcare professionals for proper use of preparations containing brimonidine tartrate would be appreciated.

[Literature]
1) Tomohiko Usui: Journal of Japanese Ophthalmological Society,2009; 113:1041-1049
2) Maruyama Y, et al.:Cornea. 2017; 36:1567-1569

[References]
•Revisions of PRECAUTIONS (PSB/PSD Notification No.0611-1 dated June 11, 2024)
https://www.mhlw.go.jp/content/001262757.pdf (in Japanese)
English translation by the PMDA (June 11, 2024)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html

•The Manuals for Management of Individual Serious Adverse Drug Reaction
https://www.mhlw.go.jp/topics/2006/11/dl/tp1122-1o09_r01.pdf (only in Japanese)

2

Recent Efforts on MID-NET®

1. Introduction

MID-NET (Medical Information Database NETwork)® is a medical information database and analysis system, and the PMDA has managed and operated it as part of its operations pursuant to the Act on the Pharmaceuticals and Medical Devices Agency (Act No.192 of 2002). Based on the Review of Pharmaceutical Administration for Prevention of Drug-induced Health Damage (final proposals) and Proposal on Drug Safety and Security Through Utilization of an Electronic Medical Information Database (Japan Sentinel Project), MID-NET® was established for the purpose of promoting pharmacoepidemiological safety measures for drugs, etc. to make up for the limitations of adverse drug reaction (ADR) reports from medical institutions and pharmaceutical companies. Establishment of MID-NET® was started in 2011, and it was launched in April 2018.

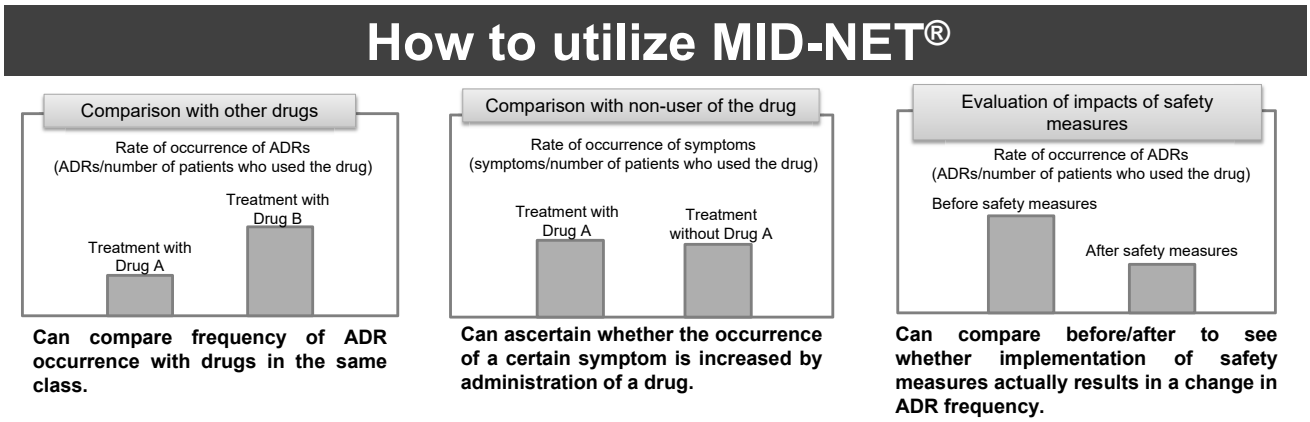
Through collaboration with 10 healthcare organizations across Japan (7 university hospitals and 3 medical institution groups), MID-NET® is capable of collecting and analyzing medical information (electronic medical record data, claim data, and Diagnosis Procedure Combination [DPC] data) on a scale exceeding 8 million patients (in total as of the end of December 2023). In addition, cooperation with the National Hospital Organization made it possible to utilize medical information on more than 12 million patients, including linked data (claim data and DPC data).

This section introduces recent efforts to improve MID-NET®. Details of the outline of MID-NET®, etc. are described in the previous article (“Pharmaceuticals and Medical Devices Safety Information No. 383"). Please refer to that article as well.

2. MID-NET®: How to utilize and the current status of utilization

We expect MID-NET® to be used as shown in Figure 1. Figure 2 shows the utilization of MID-NET® by the MHLW/PMDA, pharmaceutical companies, and academia.

(Figure 1) Example of how to utilize MID-NET®



(Figure 2) Status of MID-NET® utilization (as of the end of March 2024)

Status of MID-NET® utilization (As of the end of March 2024)

	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022	FY 2023	Total from start of operation
Regulatory utilization	33	28	26	30	30	29	176 studies
Utilization by companies (post-marketing surveillance)	2	1	1	3	3	4	14 products
Other utilization by companies/academia (studies other than post-marketing surveillance)	1	1*	1	–	–	1	4 studies

*In FY 2018, utilization of MID-NET® was approved for a study falling under the "studies other than post-marketing surveillance (without data set for analysis)" category. However, a change of its utilization category to "studies other than post-marketing surveillance (with data set for analysis)" was approved in FY 2019. Therefore, this study was counted as a study in FY 2019.

The results of the regulatory utilization (utilization by the PMDA/MHLW) are used for safety measures such as revision of PRECAUTIONS. Below is a summary of two published studies of regulatory utilization.

(1) Study on the risk assessment of hypocalcaemia in patients with renal impairment prescribed bisphosphonate preparations

Bisphosphonate preparations[*1] are widely used as the first-line drugs for osteoporosis excluding early postmenopausal osteoporosis. Precautions for the use of bisphosphonate preparations in patients with renal impairment have been included in the "CONTRAINDICATIONS" and "Careful Administration" sections of PRECAUTIONS, considering that bisphosphonate preparations have not been used in patients with renal impairment and that they are excreted renally. On the other hand, in drug use-results surveys and adverse drug reaction reports, hypocalcaemia has been reported in cases where bisphosphonate preparations were administered to patients with renal impairment. Hypocalcaemia was assumed to be an adverse drug reaction common to bisphosphonate preparations based on their pharmacological mechanism of action. However, since risks in accordance with the degree of renal impairment had not been quantitatively evaluated, a pharmacoepidemiological study was conducted using MID-NET®.

Based on the results of the study, a decision was made to issue a notification for revision of PRECAUTIONS for bisphosphonate preparations to add the results of the Japanese database study to the "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" and "Careful Administration" sections. The study showed that, among patients with renal impairment who used bisphosphonate preparations for osteoporosis, the incidence of hypocalcaemia increased particularly in patients with severe renal impairment.

*1 Alendronate sodium hydrate, ibandronate sodium hydrate, etidronate disodium, zoledronic acid hydrate, minodronic acid hydrate, and sodium risedronate hydrate

(2) Study on evaluation of the effect of antidepressants on indices of decreased platelet count

Regarding SSRIs[*2], SNRIs[*3], and vortioxetine hydrobromide, which are antidepressants, a precaution for decreased platelet count was included in the Clinically Significant Adverse Reactions section in PRECAUTIONS, or in the Other Adverse Reactions section for some drugs, while no precaution was included in either section for some of the drugs. Thus, the status of issuance of precautions differed among the drugs. In addition, no preceding studies that quantitatively evaluated the risk of decreased platelet count among the drugs had been reported. Accordingly, a pharmacoepidemiological study was conducted using MID-NET®.

Based on the results of the study and the post-marketing cases related to decreased platelet

count, a notification for revision of PRECAUTIONS for sertraline hydrochloride was issued. Specifically, a cautionary statement regarding blood tests was added in the "IMPORTANT PRECAUTIONS" section, and "decreased platelet count" was added to the "Clinically Significant Adverse Reactions" section of "ADVERSE REACTIONS."

*2 Escitalopram oxalate, sertraline hydrochloride, paroxetine hydrochloride hydrate, and fluvoxamine maleate
*3 Duloxetine hydrochloride, venlafaxine hydrochloride, and milnacipran hydrochloride

3. Past efforts to promote the use of MID-NET®

In order to operate MID-NET® rationally and efficiently from the perspective of the original business purpose of "the sophistication of safety measures," the PMDA made the three pillars of (1) Building a roadmap, (2) Improvement of accessibility, and (3) Reinforcement of regulatory utilization. These three pillars were positioned as top priorities in promotion of MID-NET® utilization, within the target period of the Fourth Mid-term Plan (from FY 2019 to FY 2023), and all of these goals have been achieved (Figure 3).

(Figure 3) Efforts to promote MID-NET® utilization

4. Further efforts to promote MID-NET® utilization

In September 2023, following "3. Past efforts to promote the use of MID-NET®," the PMDA began exchanging opinions with the users of MID-NET® or those considering its use, in an effort to improve accessibility based on the needs. In response to the content obtained through these activities, the PMDA has simplified and shortened various procedures to improve the accessibility of MID-NET®. For example, (1) the method of the MID-NET® training program has been changed from web conference to e-learning, and (2) the method of making a reservation for the on-site center has been changed from e-mail to reservation on the website.

Moreover, (3) the MID-NET® connecting environment (environment that allows remote connection from a company office, etc. to the data center) has been changed to enable easier connections, and (4) the scope of use has been expanded. The PMDA will continue to improve MID-NET® to meet the needs of users. The PMDA has also initiated the following extensive modification of MID-NET® operations to accommodate use by cooperating medical institutions and academia: (5) Provision of aggregate information to those who are preparing study protocols on

the premise of utilizing MID-NET® (e.g., aggregated values such as the number of patients necessary to assess the feasibility of utilizing MID-NET®) (free of charge), and, for use in studies of public interest, (6) year-round acceptance of applications for use and (7) accommodation of the MID-NET® connecting environments for these users.

These efforts are expected to promote the use of MID-NET® by a wide range of users, including pharmaceutical companies and academia.

In order to contribute to pharmaceutical safety measures utilizing medical information databases, the PMDA will continue to promote further use of MID-NET® through efforts to improve accessibility based on the needs of pharmaceutical companies, etc.

5. Closing remark

In our country, utilization of medical information databases for the purpose of drug evaluation has just begun. The PMDA will continue to proactively promote drug evaluation using medical information databases. The PMDA will play a role in further ensuring drug safety and promotion of proper use through safety measures utilizing medical information databases such as MID-NET®.

Your understanding of safety measures utilizing MID-NET®, etc. as well as your continued cooperation for the proper use of drugs would be appreciated.

[References]

• PMDA website: MID-NET® (Medical Information Database)
https://www.pmda.go.jp/safety/mid-net/0001.html (only in Japanese)
• PMDA website: Studies conducted by the PMDA
https://www.pmda.go.jp/safety/surveillance-analysis/0045.html (only in Japanese; some study reports are available in English as follows.)
Database study using MID-NET® on risk assessment of hypocalcaemia in patients with renal impairment prescribed bisphosphonate preparations
https://www.pmda.go.jp/files/000249791.pdf
Evaluation of the effect of antidepressants on indices of decreased platelet count using MID-NET®
https://www.pmda.go.jp/files/000265893.pdf
• Pharmaceuticals and Medical Devices Safety Information No. 383
https://www.pmda.go.jp/files/000241005.pdf (in Japanese)
https://www.pmda.go.jp/files/000241088.pdf (in English)

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated June 11, 2024, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 [1] Brimonidine tartrate
[2] Brimonidine tartrate/timolol maleate
[3] Brimonidine tartrate/brinzolamide
[4] Ripasudil hydrochloride hydrate/brimonidine tartrate

Brand name (name of company)	[1] Aiphagan Ophthalmic Solution 0.1% (Senju Pharmaceutical Co., Ltd.), and the others [2] Aibeta Combination Ophthalmic Solution (Senju Pharmaceutical Co., Ltd.) [3] Ailamide Combination Ophthalmic Suspension (Senju Pharmaceutical Co., Ltd.) [4] Gla-alpha combination ophthalmic solution (Kowa Company, Ltd.)
Therapeutic category	Agents for ophthalmic use
Indications	[1] Glaucoma and ocular hypertension when other glaucoma drugs are not sufficiently effective or cannot be used [2][3][4] Glaucoma and ocular hypertension in patients who have not responded sufficiently to other anti-glaucoma drugs

PRECAUTIONS (Revised language is underlined.)

•Brimonidine tartrate

•Brimonidine tartrate/brinzolamide

•Ripasudil hydrochloride hydrate/brimonidine tartrate

8. IMPORTANT PRECAUTIONS (newly added)	Corneal opacity with neovascularisation, etc. may occur following administration of this drug. Patients should consult their doctor periodically, and they should be carefully monitored. In addition, they should be adequately instructed to seek medical attention immediately if they have any subjective symptoms such as hyperaemia, reduced visual acuity, or blurred vision.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	11.1 Clinically Significant Adverse Reactions Corneal opacity

•Brimonidine tartrate/timolol maleate

8. IMPORTANT PRECAUTIONS (newly added)	Corneal opacity with neovascularisation, etc. may occur following administration of this drug. Patients should consult their doctor periodically, and they should be carefully monitored. In addition, they should be adequately instructed to seek medical attention immediately

	if they have any subjective symptoms such as hyperaemia, reduced visual acuity, or blurred vision.
11. ADVERSE REACTIONS	Corneal opacity
11.1 Clinically Significant Adverse Reactions (newly added)	
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving corneal opacity: [1] 9 cases, including 2 cases in which the drug was administered outside the approved indications or dosage and administration (No patient mortalities) [2] 0 [3] 3 (No patient mortalities) [4] 0 Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 180,807 [2] Approximately 46,070 [3] Approximately 294,669 [4] Approximately 50,000 Japanese market launch: [1] May 2012 [2] December 2019 [3] June 2020 [4] December 2022

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 60s	Glaucoma (cataract)	Unknown for approximately 5 years	**Corneal opacity, blurred vision, reduced visual acuity, corneal neovascularisation, conjunctival hyperaemia**	
				Day 1 of administration	The patient received treatment for both eyes with the three drugs latanoprost, brinzolamide/timolol maleate combination drug and brimonidine tartrate for glaucoma at the previous hospital.
				Approximately 1 year after administration	The drugs were changed to the three drugs bimatoprost, brinzolamide/timolol maleate combination drug, and brimonidine tartrate.
				Approximately 5 years after administration (day of onset)	The patient noticed reduced visual acuity in his right eye, and vascular invasion into the cornea and corneal opacity began to be noted. In the same year, he was referred to a university hospital for further examination of the cause and treatment. For the anterior segment, fan-shaped opacity at the temporal and nasal corneal periphery and vascular invasion from the deep stroma to the central part were found in the right eye, opacity at the peripheral cornea and at superior part and vascular invasion from the periphery were found in the left eye, and distinct conjunctival hyperaemia was found in both eyes. There were no other findings such as keratic precipitates, corneal/conjunctival epithelium defect, palpebral/conjunctival follicles or blepharitis. Mild cataract was observed in both eyes. Corneal opacity due to brimonidine tartrate was suspected because he had no past history that could cause interstitial keratitis and no other abnormal findings that could cause reduced visual acuity were noted. He was instructed to continue instillation of the two drugs bimatoprost and brinzolamide/timolol maleate combination drug and to discontinue instillation of brimonidine tartrate. He was instructed to instill betamethasone sodium phosphate 3 times daily into both eyes.
				14 days after the first visit (day of discontinuation of administration)	Although the patient had been instructed to discontinue brimonidine tartrate at the initial visit to the university hospital, it was found that he was still instilling brimonidine tartrate. However, the corrected visual acuity improved to 0.6p in the right eye and 1.2 in the left eye. An anterior segment OCT showed opacity mainly in the middle layer of the corneal stroma. Limbal hyperaemia in the right eye showed a tendency to improve, and the corneal stromal opacity appeared to be paler on slit-lamp microscopy than at the initial visit to the university hospital. The slit-lamp microscopic findings showed that the corneal opacity in the left eye had disappeared. He was again instructed to discontinue eye instillation of brimonidine tartrate and to continue instillation of betamethasone sodium phosphate.

				14 days after discontinuation of administration	The corrected visual acuity improved to 0.7p in the right eye and 1.2 in the left eye. The intraocular pressure increased to 30 mmHg in the right eye and 45 mmHg in the left eye. A slit-lamp microscopy revealed that the opacity of the right eye became slightly paler. An anterior segment OCT showed opacity lesions mainly in the middle layer of the corneal stroma, but the opacity area slightly diminished compared with the previous examination, and the opacity itself also became less opaque. For the increased intraocular pressure, instillation of ripasudil hydrochloride hydrate twice daily was additionally started while bimatoprost and brinzolamide/timolol maleate combination drug were continued. While discontinuing instillation of betamethasone sodium phosphate, instillation of fluorometholone 3 times daily was started. The patient was instructed to visit the hospital again 4 days later.
				18 days after discontinuation of administration	Although the opacity decreased slightly, the intraocular pressure remained high (31.0 mmHg in the right eye and 35.0 mmHg in the left eye). Considering the possibility of being a steroid responder, fluorometholone was discontinued and oral administration of a carbonic anhydrase inhibitor twice daily was started.
				28 days after discontinuation of administration	The intraocular pressure decreased to 20 mmHg in the right eye and 21 mmHg in the left eye. The corrected visual acuity of the right eye increased to 1.0, and the corneal opacity became slightly less opaque.
				105 days after discontinuation of administration	The patient was followed up. There was no remarkable change in the extent of the opacity. The visual acuity and intraocular pressure were stable. Although the corneal opacity remained, the subjective symptoms improved and the visual acuity also stabilized. Therefore, the patient underwent further follow up at the previous hospital, and the examination at the university hospital was completed.
	Concomitant drugs: Bimatoprost, brinzolamide/timolol maleate combination drug, latanoprost				

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Male 70s	Normal tension glaucoma (hypertension, emphysema, cataract)	1 drop, twice for 496 days	**Corneal opacity**	
				Approximately 5 years before administration	Latanoprost was administered in both eyes to treat glaucoma.
				Approximately 32 months before administration	Brimonidine tartrate was administered in the right eye for glaucoma.
				Day 1 of administration	Administration of brimonidine tartrate was discontinued, and then administration of brimonidine tartrate/brinzolamide in the right eye was initiated.
				Approximately 15 months after administration	Strong pruritus in the right eye occurred.
				Approximately 16 months after administration (day of onset)	At a routine visit to the previous hospital, it was noted that corrected visual acuity of the right eye had decreased to 0.2. Intraocular pressure was 16/11 mmHg. Superficial punctate keratitis in the right eye and fan-like-patterned corneal opacity in the nasal cornea were noted. Neovascularisation was observed in the deep lamellar cornea at the site of corneal opacity. Hyperaemia and follicles were observed in the conjunctiva. Latanoprost and brimonidine tartrate/brinzolamide had been administered in both eyes and in the right eye, respectively. Therefore, administration of brimonidine tartrate/brinzolamide was discontinued and administration of betamethasone sodium phosphate and gatifloxacin hydrate in the right eye was initiated.
				18 days after discontinuation	The patient visited a university hospital. Corrected visual acuity of the right eye was 0.4. Corneal opacity improved mildly.
				52 days after discontinuation	Corrected visual acuity of the right eye improved to 0.7. Corneal opacity was gradually alleviated with opacity at the endothelial side of the cornea remaining. Conjunctival findings returned to normal.
				87 days after discontinuation	The corneal opacity resolved, but with sequelae (remaining corneal opacity).
	Concomitant drugs: Latanoprost				

4

Revisions of PRECAUTIONS (No. 351)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated May 17, June 11, 2024.

1 Other antitumor agents

Pembrolizumab (genetical recombination)

Brand name	Keytruda Injection 100 mg (MSD K.K.)
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	<Unresectable, advanced or recurrent non-small cell lung cancer> When this drug is co-administered with other antineoplastic drugs, the other antineoplastic drugs to be administered should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <Recurrent or metastatic head and neck cancer> Dosage and administration of this drug should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section and with full understanding of efficacy and safety of this drug. In addition, when this drug is co-administered with other antineoplastic drugs, the other antineoplastic drugs to be administered should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <Radically unresectable or metastatic renal cell carcinoma> Other antineoplastic drugs to be co-administered should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer> Other antineoplastic drugs to be co-administered should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <Pre- and postoperative adjuvant therapy for hormone receptor-negative and HER2-negative breast cancer at high risk of recurrence> Dosage and administration of this drug should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section. In addition, other antineoplastic drugs to be co-administered should be selected with a thorough understanding of the contents of the 17. CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <Unresectable, advanced or recurrent gastric cancer> Other antineoplastic drugs to be co-administered should be selected with a thorough understanding of the contents of the 17. CLINICAL

	STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources.

2 Agents for ophthalmic use

[1] Brimonidine tartrate
[2] Brimonidine tartrate/brinzolamide
[3] Ripasudil hydrochloride hydrate/brimonidine tartrate

Brand name	[1] Aiphagan Ophthalmic Solution 0.1% (Senju Pharmaceutical Co., Ltd.), and the others [2] Ailamide Combination Ophthalmic Suspension (Senju Pharmaceutical Co., Ltd) [3] Gla-alpha combination ophthalmic solution (Kowa Company, Ltd.)
8. IMPORTANT PRECAUTIONS (newly added)	Corneal opacity with neovascularisation, etc. may occur following administration of this drug. Patients should consult their doctor periodically, and they should be carefully monitored. In addition, they should be adequately instructed to seek medical attention immediately if they have any subjective symptoms such as hyperaemia, reduced visual acuity, or blurred vision.
11. ADVERSE REACTIONS (newly added)	11.1 Clinically Significant Adverse Reactions Corneal opacity

3 Agents for ophthalmic use

Brimonidine tartrate/timolol maleate

Brand name	Aibeta Combination Ophthalmic Solution (Senju Pharmaceutical Co., Ltd.)
8. IMPORTANT PRECAUTIONS (newly added)	Corneal opacity with neovascularisation, etc. may occur following administration of this drug. Patients should consult their doctor periodically, and they should be carefully monitored. In addition, they should be adequately instructed to seek medical attention immediately if they have any subjective symptoms such as hyperaemia, reduced visual acuity, or blurred vision.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Corneal opacity

4 Other cardiovascular agents

Finerenone

Brand name	Kerendia tablets 10 mg, 20 mg (Bayer Yakuhin, Ltd.)
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	Patients receiving the following drugs: Itraconazole, posaconazole, voriconazole, preparations containing ritonavir, atazanavir, darunavir, fosamprenavir, preparations containing cobicistat, clarithromycin, ensitrelvir

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Itraconazole Posaconazole Voriconazole Preparations containing ritonavir Atazanavir Darunavir Fosamprenavir Preparations containing cobicistat Clarithromycin Ensitrelvir	The blood concentration of finerenone may increase markedly.	The clearance of finerenone is decreased by the potent inhibition of CYP3A.

5 Agents affecting metabolism, n.e.c. (not elsewhere classified)

Carglumic acid

Brand name
Carbaglu dispersible tablets 200 mg (Recordati Rare Diseases Japan K.K.)

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION (newly added)
<Common to all indications>
The starting dose should be reduced in patients with moderate or severe renal impairment. It is recommended to start administration referring to the following: 50 mg to 125 mg per kg of body weight per day in patients with moderate renal impairment (eGFR greater than or equal to 30 and less than 60 mL/min/1.73 m^2); 15 mg to 40 mg per kg of body weight per day in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2).

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS (newly added)
9.2 Patients with Renal Impairment
Patients with moderate or severe renal impairment (eGFR less than 60 mL/min/1.73 m^2)
The starting dose should be reduced. The blood concentration of this drug may increase due to delayed renal excretion.

6 Antibiotic preparations acting mainly on mold

Posaconazole

Brand name
Noxafil Tablets 100 mg, Noxafil for Intravenous Infusion 300 mg (MSD K.K.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving the following drugs: Ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, methylergometrine, ergometrine, simvastatin, atorvastatin, pimozide, quinidine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], suvorexant, finerenone, lurasidone hydrochloride, blonanserin, triazolam, rivaroxaban

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors

Finerenone	The effect of finerenone may be enhanced.	The plasma concentration of finerenone is expected to rise due to the inhibition of CYP3A4 by co-administration with posaconazole.

7 Antibiotic preparations acting mainly on mold

Voriconazole

Brand name

Vfend Tablets 50 mg, 200 mg, Vfend for Intravenous Use 200 mg, Vfend Dry Syrup 2800 mg (Pfizer Japan Inc.), and the others

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

Patients receiving the following drugs: Rifampicin, rifabutin, efavirenz, ritonavir, lopinavir/ritonavir, nirmatrelvir/ritonavir, carbamazepine, barbital, phenobarbital, pimozide, quinidine, ivabradine, ergot alkaloids (ergotamine/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, ergometrine, methylergometrine), triazolam, ticagrelor, asunaprevir, lomitapide, blonanserin, suvorexant, rivaroxaban, riociguat, azelnidipine, olmesartan medoxomil/azelnidipine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], anamorelin, lurasidone, isavuconazonium, finerenone

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Finerenone	The blood concentration of finerenone may rise and the effect of finerenone may be enhanced by co-administration with voriconazole.	Voriconazole inhibits the metabolizing enzyme of finerenone (CYP3A4).

5

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 May 31, 2024)
◎: Products for which EPPV was initiated after May 1, 2024

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Recombinant respiratory syncytial virus vaccine[*1] / Abrysvo intramuscular injection	Pfizer Japan Inc.	May 31, 2024
◎	Lebrikizumab (genetical recombination) / Ebglyss Subcutaneous Injection Syringes 250 mg, Ebglyss Subcutaneous Injection Autoinjectors 250 mg	Eli Lilly Japan K.K.	May 31, 2024
◎	Apadamtase alfa (genetical recombination)/ cinaxadamtase alfa (genetical recombination) / Adzynma Intravenous 1500	Takeda Pharmaceutical Company Limited	May 30, 2024
◎	Cysteamine hydrochloride / Cystadrops Ophthalmic Solution 0.38%	Viatris Pharmaceuticals Japan Inc.	May 30, 2024
◎	Lonafarnib / Zokinvy capsules 50 mg, 75 mg	AnGes, Inc.	May 27, 2024
◎	Elranatamab (genetical recombination) / Elrexfio S.C. Injection 44 mg, 76 mg	Pfizer Japan Inc.	May 22, 2024
◎	Capivasertib / Truqap tablets 160 mg, 200 mg	AstraZeneca K.K.	May 22, 2024
◎	Nirsevimab (genetical recombination) / Beyfortus 50 mg solution for intramuscular injection in syringe, Beyfortus 100 mg solution for intramuscular injection in syringe	AstraZeneca K.K.	May 22, 2024
◎	Belumosudil mesilate / Rezurock Tablets 200 mg	Meiji Seika Pharma Co., Ltd.	May 22, 2024
◎	Crovalimab (genetical recombination) / Piasky for Injection 340 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2024

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Sacubitril valsartan sodium hydrate[*2] Entresto Granules for Pediatric 12.5 mg, 31.25 mg	Novartis Pharma K.K.	May 22, 2024
◎	Luspatercept (genetical recombination) Reblozyl for S.C. injection 25 mg, 75 mg	Bristol-Myers Squibb K.K.	May 20, 2024
◎	Letermovir[*3] Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 17, 2024
	Talazoparib tosilate (1) Talzenna capsules 0.1 mg, (2)Talzenna capsules 0.25 mg, (3) Talzenna capsules 1 mg	Pfizer Japan Inc.	April 23, 2024
	Evinacumab (genetical recombination) Evkeeza for Intravenous Infusion 345 mg	Ultragenyx Japan K.K.	April 17, 2024
	Danicopan Voydeya tablets 50 mg	Alexion Pharma Godo Kaisha	April 17, 2024
	Aflibercept (genetical recombination) Eylea 8mg solution for IVT inj. 114.3 mg/mL	Bayer Yakuhin, Ltd.	April 17, 2024
	Efgartigimod alfa (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Vyvdura Combination Subcutaneous Injection	argenx Japan K.K.	April 17, 2024
	Perampanel hydrate Fycompa for intravenous infusion 2 mg	Eisai Co., Ltd.	April 17, 2024
	Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	March 26, 2024
	Rifaximin Rifxima Tablets 200 mg	Aska Pharmaceutical Co., Ltd.	March 26, 2024
	Fenfluramine hydrochloride[*4] Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	March 26, 2024
	Efgartigimod alfa (genetical recombination)[*5] Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	March 26, 2024
	Baricitinib[*6] (1) Olumiant tablets 2 mg, (2) Olumiant tablets 4 mg	Eli Lilly Japan K.K.	March 26, 2024
	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Gobik Aqueous Suspension Syringes	The Research Foundation for Microbial Diseases of Osaka University	March 15, 2024
	Adsorbed diphtheria-purified pertussis-	KM Biologics Co., Ltd.	March 14,

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Quintovac Aqueous Suspension Injection		2024
Semaglutide (genetical recombination)[*7] (1) Wegovy Subcutaneous Injection 0.25 mg SD, (2) Wegovy Subcutaneous Injection 0.5 mg SD, (3) Wegovy Subcutaneous Injection 1.0 mg SD, (4) Wegovy Subcutaneous Injection 1.7 mg SD, (5) Wegovy Subcutaneous Injection 2.4 mg SD	Novo Nordisk Pharma Ltd.	February 22, 2024
Tenapanor hydrochloride Phozevel Tablets 5mg, 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	February 20, 2024
Zilucoplan sodium Zilbrysq Syringe for S.C. Injections 16.6 mg, 23.0 mg, 32.4 mg	UCB Japan Co. Ltd.	February 16, 2024
Concizumab (genetical recombination) Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	February 16, 2024
Sacubitril valsartan sodium hydrate[*8] (1) Entresto Tablets 50 mg, (2) Entresto Tablets 100 mg, (3) Entresto Tablets 200 mg	Novartis Pharma K.K.	February 9, 2024
Empagliflozin[*9] Jardiance Tablets 10 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 9, 2024
pH4-treated acidic normal human immunoglobulin (subcutaneous injection) Cuvitru 20% S.C. Injection 2 g/10 mL, 4 g/20 mL, 8 g/40 mL	Takeda Pharmaceutical Company Limited	January 24, 2024
Recombinant respiratory syncytial virus vaccine Arexvy Intramuscular Injection	GlaxoSmithKline K.K.	January 15, 2024
Glucarpidase (genetical recombination) Megludase for Intravenous Use 1000	Ohara Pharmaceutical Co., Ltd.	January 4, 2024
Bimekizumab (genetical recombination)[*10] Bimzelx Syringe for S.C. injection 160 mg, Bimzelx Autoinjector for S.C. injection 160 mg	UCB Japan Co. Ltd.	December 22, 2023
Eltrombopag olamine Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	December 22, 2023
Brexpiprazole[*11] Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	December 22, 2023
Cefiderocol tosilate sulfate hydrate Fetroja for Intravenous Drip Infusion 1 g	Shionogi & Co., Ltd.	December 20, 2023
Lecanemab (genetical recombination) Leqembi for Intravenous Infusion 200 mg, 500 mg	Eisai Co., Ltd.	December 20, 2023

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	Difelikefalin acetate Korsuva IV Injection Syringe for Dialysis 17.5 μg, 25.0 μg, 35.0 μg	Maruishi Pharmaceutical Co., Ltd.	December 13, 2023
	Coronavirus (SARS-CoV-2) RNA vaccine*12 Daichirona for Intramuscular Injection	Daiichi Sankyo Co., Ltd.	December 1, 2023

*1 Prevention of infections caused by RS virus in individuals aged 60 years and older

*2 Addition of a pediatric dosage indicated for chronic heart failure

*3 Prophylaxis of cytomegalovirus infections in organ transplant recipients

*4 Concomitant therapy with antiepileptic drugs for epileptic seizures in patients with Lennox-Gastaut syndrome who are not sufficiently responsive to other antiepileptic drugs

*5 Chronic idiopathic thrombocytopenic purpura

*6 Polyarticular-course juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional treatments

*7 Treatment of obesity
The use is limited to patients with either hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not adequately responded to treatment with diet and exercise therapy and meet the following conditions:
•BMI of 27 kg/m^2 or greater in the presence of at least two obesity-related comorbidities
•BMI of 35 kg/m^2 or greater

*8 Addition of pediatric dosage indicated for chronic heart failure

*9 Chronic kidney disease

*10 Psoriatic arthritis (PsA), ankylosing spondylitis (AS), and non-radiographic axial spondyloarthritis (nr-axSpA) in patients who have not sufficiently responded to conventional therapies

*11 Depression/depressed state (for use only in patients who have not sufficiently responded to conventional antidepressant therapies)

*12 Prevention of infectious disease caused by SARS-CoV-2