Pharmaceuticals and Medical Devices Safety Information

No. 413 September 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.

Register here

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100-8916 Japan

Pharmaceuticals and Medical Devices Safety Information

No. 413 September 2024

Ministry of Health, Labour and Welfare
Pharmaceutical Safety 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 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

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.

Abbreviations

ADR	Adverse Drug Reaction
aHR	Adjusted Hazard Ratio
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DB	Deep Burn
DIC	Disseminated Intravascular Coagulation
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPPV	Early Post-marketing Phase Vigilance
KDIGO	Kidney Disease Improving Global Outcomes
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
OTC	Over-the-Counter
PASS	Post-authorisation Safety Study
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division
TBSA	Total Body Surface Area

1

Revision of PRECAUTIONS for Sodium Valproate

1. Introduction

Sodium valproate, for which marketing in Japan was initiated in March 1975, is the drug indicated for “treatment of various types of epilepsy (petit mal, focal seizure, psychomotor seizures, and mixed seizure) and personality or behaviour disorders (bad mood, irritability, etc.) associated with epilepsy,” ”treatment of mania and manic state in manic depressive illness,” and “prevention of migraine attacks.”

As a result of the investigation including the opinions of experts regarding the possible occurrence of neurodevelopmental disorder in infants/children with paternal exposure to sodium valproate, the MHLW considered it necessary to take safety measures, and issued a notification instructing the marketing authorization holders (MAHs) to revise PRECAUTIONS on August 27, 2024. This section will introduce the details of the review.

2. Background

The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) made a set of recommendations necessitating the revision of the product information to add a precaution for the potential risk of neurodevelopmental disorder in infants/children with paternal exposure to sodium valproate on the basis of the non-interventional post-authorisation safety study (hereinafter referred to as “PASS”) imposed on the MAHs of valproic acid preparations by the EMA.

Also in Japan, on the basis of the overseas epidemiological literature in addition to the PASS, the necessity of revising the Japanese electronic package insert was discussed.

3. Details of the review

The PASS and published articles on overseas epidemiological studies were evaluated. As a result, considering the results of the following 2 studies, the MHLW/PMDA concluded that the possibility of occurrence of neurodevelopmental disorder in infants/children with paternal exposure to sodium valproate cannot be ruled out, although the evaluation of the risk of neurodevelopmental disorder in infants/children with paternal exposure to sodium valproate has not been established:

- In the cohort study using data from national registries of 3 Scandinavian countries, which was a PASS, the adjusted hazard ratio (aHR) of neurodevelopmental disorder was 1.50 (95% CI: 1.09−2.07) in infants/children with paternal exposure to valproate in the 3 months preconception period (valproate group) compared to those with paternal exposure to lamotrigine or levetiracetam in the 3 months preconception period (control group).[1)] In this study, a significantly increased risk of neurodevelopmental disorder was observed in the valproate group. However, the study had limitations such as the possibility of confounding and a longer follow-up period in the valproate group compared to the control group.
- In the cohort study using health register and social register data in Denmark, aHR of neurodevelopmental disorder was 1.10 (95% CI: 0.88-1.37) in infants/children with paternal exposure to valproate within 120 days prior to conception (exposed children) compared with those with no paternal exposure to valproate (unexposed children). In addition, in the case of fathers with epilepsy, aHR for children exposed to valproate was 1.09 (95% CI: 0.85-1.39) compared with unexposed children. In both cases, no significantly increased risk of neurodevelopmental disorder was observed in children exposed to valporate.[2)]

Regarding the PASS conducted in Europe, performing a new study for further investigation has been required, taking the study's limitations into consideration.[3)] Although the risk of neurodevelopmental disorder in infants/children with paternal exposure to sodium valproate has not been fully evaluated at this point, the new information, which indicates that the impact of the administration of sodium valproate to fathers on neurodevelopment in infants/children cannot be ruled out, was considered to be a potential risk. Therefore, it was decided to provide information in the OTHER PRECAUTIONS section in the electronic package insert to inform the healthcare professionals of both reports with and without a statistically significant increased risk.

4. Closing remark

Healthcare professionals are requested to understand the purpose of this revision and to carefully review the electronic package inserts to make an informed decision. Continued cooperation by healthcare professionals for proper use would be appreciated.

[References]
1) PASS -Paternal exposure to valproate -Updated Abstract Following Reanalysis of Norway Data of Corrigendum to Final Study Report Version 1.1 and Addendum Version 2 Valproate EU consortium Stand Alone Abstract V2.0: https://catalogues.ema.europa.eu/system/files/2024-02/Valproate_PASS_Abstract_V2.0_0.pdf
2) Christensen J, et al.: JAMA Netw Open. 2024; 7: e2414709
3) Assessment report by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA): https://www.ema.europa.eu/en/documents/other/valproate-prac-non-interventional-imposed-pass-final-study-report-assessment-report-emea-h-n-psr-j-0043_en.pdf

[Reference information]
•Revision of PRECAUTIONS (PSB/PSD Notification No. 0827-1 dated August 27, 2024)
https://www.mhlw.go.jp/content/001295071.pdf (in Japanese)
English translation by the PMDA (August 27, 2024)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html (in English)

2

Revision of Precautions for Mirogabalin Besilate

1. Introduction

Mirogabalin besilate (hereinafter referred to as “mirogabalin”) is a drug indicated for “neuropathic pain,” and its marketing was initiated in April 2019.

As a result of the investigation, including the opinions of expert advisors, regarding the possible occurrence of renal impairment in patients treated with mirogabalin, the MHLW considered it necessary to take safety measures, and instructed the MAHs to revise the PRECAUTIONS on August 27, 2024. The details of the review are described in this section.

2. Background

After the marketing of mirogabalin in Japan, cases of renal impairment developing after administration of mirogabalin have been reported. Based on the reported cases, a study using MID-NET®, a medical information database, was conducted. Taking into account the cases reported in Japan, the results of the study using MID-NET®, etc., the necessity of revision of the electronic package insert in Japan was deliberated. Mirogabalin is marketed in several Asian countries including Japan, but it has not been approved in Europe or the United States.

3. Details of the review

(1) Post-marketing cases reported in Japan

Of the Japanese cases involving renal impairment that developed after administration of mirogabalin, the MHLW/PMDA have confirmed 3 reported cases for which a causal relationship with mirogabalin was reasonably possible. However, in some of these cases, patients with existing decreased kidney function developed rapid worsening in kidney function after administration of mirogabalin. Although there was a temporal relationship with mirogabalin, the primary disease was also considered to have affected it in these cases.

(2) Study using MID-NET®

A study using MID-NET® (hereinafter referred to as “this study”) was conducted as signal enhancement of routine monitoring of early signals on drug safety because renal impairment due to mirogabalin had been reported in post-marketing cases in Japan. The main results are as follows:

- The incidence of kidney function test abnormal after prescription of mirogabalin besilate was compared with that after prescription of an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus (for oral use), for which no precautions for renal impairment-related events were included in the Clinically Significant Adverse Reactions section of the electronic package insert. In the analysis performed limited to patients with baseline kidney function test values within the reference range,[*1] the lower limit of the 95% confidence interval for the sex and age-adjusted hazard ratio of mirogabalin exceeded 1 for each of the defined outcomes (see Table 1).[1)]
- The incidence of kidney function test abnormal after prescription of mirogabalin besilate was compared with that after prescription of pregabalin, for which a precaution for “renal failure” had already been included in the “Clinically Significant Adverse Reactions” section of the electronic package insert. In the analysis performed limited to patients with baseline renal function test values within the reference range,[*1] the sex and age-adjusted hazard ratio of

mirogabalin exceeded 1 when outcome definitions shown in Table 1 below (decreased eGFR [< 30] and increased serum creatinine [with reference to acute kidney injury stage 3 in the KDIGO Clinical Practice Guideline[*2]]) were used.[2)]

Table 1. Incidence rate of kidney function test abnormal in mirogabalin and comparator, and sex and age-adjusted hazard ratios of the exposure in comparison with the comparator (in patients with baseline renal function test values within the reference range[*1])

		Literature 1		Literature 2	
Outcomes	Evaluation indices	Mirogabalin (n=7,137)	An extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus (for oral use) (n=5,160)	Mirogabalin (n=3,459)	Pregabalin (n=18,559)
Decreased eGFR (< 30)	Incidence rate of outcome (/1000 person-years)	39.454	11.408	46.446	32.572
	Sex and age-adjusted hazard ratio (95% confidence interval)	3.54 (2.25−5.58)	Reference	1.32 (0.99−1.77)	Reference
Increased serum creatinine (with reference to acute kidney injury stage 3 in the KDIGO Clinical Practice Guideline[*2])	Incidence rate of outcome (/1000 person-years)	23.312	5.935	28.142	21.848
	Sex and age-adjusted hazard ratio (95% confidence interval)	3.80 (2.06−7.01)	Reference	1.17 (0.81−1.69)	Reference

eGFR: estimated glomerular filtration rate

*1 eGFR ≥ 60 mL/min/1.73 m^2. The baseline value was defined as a test result on the closest to the first prescription date within 180 days before or at the first prescription date.

*2 KDIGO (Kidney Disease Improving Global Outcomes) Clinical Practice Guideline for Acute Kidney Injury

This study, which was conducted as routine monitoring of early signals on drug safety as aforementioned, has some limitations in terms of precision because the relationship between mirogabalin and the outcome was examined promptly and in an exploratory manner, and only some patient backgrounds were adjusted. However, mirogabalin and the comparator (an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus (for oral use) or pregabalin) have a similar clinical positioning in that they are the first- or second-line drugs for neuropathic pain; therefore, patient backgrounds do not seem to be significantly different between mirogabalin and the comparators. The results of this study suggested a relationship between mirogabalin and renal impairment, and the magnitude of association was possibly similar to that for pregabalin.

What is routine monitoring of early signals on drug safety?

Routine monitoring of early signals on drug safety is intended to accumulate information on the safety of drugs from an early stage and refers to an exploratory study which is performed based on common study plans in order to obtain information on the safety promptly and efficiently. In confirmatory studies, patient backgrounds (age, sex, concomitant drugs, complications, severity, etc.) are typically adjusted and analyzed based on pharmacoepidemiological methods for comparison. However, such adjustments are not made strictly in routine monitoring of early signals on drug safety. Thus, results should be carefully evaluated, and even if a signal is detected, it does not necessarily mean that there is an immediate safety concern for a drug (a causal relationship between the drug and adverse event).

The results of routine monitoring of early signals on drug safety should be utilized as one piece of the information that contributes to safety measures. The MHLW/PMDA evaluate information obtained from various sources together, such as case reports on adverse drug reactions and literature information, to implement appropriate safety measures.

(3) Situation of issuing precautions in Japan and overseas for the drugs with the same mechanism of action as mirogabalin

Precautions for “renal failure” and “acute kidney injury” are listed in the "11.1 Clinically Significant Adverse Reactions" section of the Japanese electronic package inserts for pregabalin and gabapentin[*3], respectively, which have the same mechanism of action as mirogabalin (voltage-dependent calcium channel $\alpha_2\delta$ subunit ligands). As for the overseas product labeling, the U.S. product labeling of pregabalin includes a precaution for acute kidney failure, and EU product labeling of pregabalin includes a precaution for renal failure. Although there is no relevant description in the U.S. product labeling of gabapentin, the U.K. product labeling of gabapentin includes a precaution for acute renal failure.

*3 The indication of gabapentin in Japan is “adjunctive therapy with other antiepileptic drugs to treat partial seizures (including secondary generalized seizures) in patients with epilepsy who have not responded sufficiently to other antiepileptic drugs.”

As described above, based on a comprehensive judgement of the cases reported in Japan, the results of the study using MID-NET® and the situations of issuing precautions in Japan and overseas for the drugs with the same mechanism of action, the MHLW/PMDA decided to add “renal impairment” to the Clinically Significant Adverse Reactions section of the electronic package insert of mirogabalin to call attention.

Healthcare professionals are requested to pay careful attention to the onset of renal impairment after administration of mirogabalin. They are also requested to adjust the dose and dosing interval according to the kidney function and to carefully monitor the patient’s condition after administration because adverse reactions may occur more easily, particularly when mirogabalin is administered to patients with decreased kidney function.

4. Closing remark

Healthcare professionals are encouraged to understand the purpose of this revision and to carefully review the electronic package inserts to make an informed decision. Continued cooperation by healthcare professionals for proper use of mirogabalin would be appreciated.

[Literatures]

1) Summary of investigation on the risk of kidney function test abnormal using MID-NET® (in comparison with an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus (for oral use)):
   https://www.pmda.go.jp/files/000270053.pdf (in Japanese)
   https://www.pmda.go.jp/files/000270054.pdf (in English)
2) Summary of investigation on the risk of kidney function test abnormal using MID-NET® (in comparison with pregabalin):
   https://www.pmda.go.jp/files/000270049.pdf (in Japanese)
   https://www.pmda.go.jp/files/000270052.pdf (in English)

[References]

- Revision of PRECAUTIONS (PSB/PSD Notification No. 0827-1 dated August 27, 2024)
  https://www.mhlw.go.jp/content/001295071.pdf (in Japanese)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html (in English)
- Routine monitoring of early signals on drug safety
  https://www.pmda.go.jp/safety/surveillance-analysis/0049.html (only in Japanese)

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated August 27, 2024, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Mirogabalin besilate

Brand name (name of company)	Tarlige Tablets 2.5 mg, 5 mg, 10 mg, 15 mg, Talige OD Tablets 2.5 mg, 5 mg, 10 mg, 15 mg (Daiichi Sankyo Co., Ltd.)
Therapeutic category	Other agents affecting central nervous system
Indications	Neuropathic pain

PRECAUTIONS (Revised language is underlined.)

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

Renal impairment

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 and retrieved by the following conditions:

·Cases which correspond to MedDRA version 27.0 SMQ “Acute renal failure” (broad) or SOC “Renal and urinary disorders”

·Cases whose duration of administration of this drug is described

·Cases with laboratory test results of serum creatinine of 1.07 m/dL or higher for men and 0.79 mg/dL or higher for women, estimated GFR/creatinine clearance of less than 90 mL/min/1.73 m^2, proteinuria 2+ or urinary protein/urine creatinine ratio>0.5 (equivalent to grade 1 or higher by the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) after the initiation of administration

Cases involving renal impairment reported in Japan: 3 (No patient mortality)

Number of patients using the drug as estimated by the MAH during the previous 1-year period:
Talige OD Tablets 2.5 mg: 944,633
Talige OD Tablets 5 mg: 1,902,009
Talige OD Tablets 10 mg: 419,031
Talige OD Tablets 15 mg: 128,157

Japanese market launch:
Tablets: April 2019
OD Tablets: May 2023

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 80s	Sciatic nerve neuropathy, sciatica (chronic renal failure)	2.5 mg for 6 days ↓ 5 mg for 30 days	**Renal failure**	
				Day 1 of administration	The patient started taking 2.5 mg of mirogabalin besilate once daily for sciatica.
				3 days after administration	Renal failure, hepatic function disorder, increased inflammatory reaction, and generalised oedema were noted. The patient was treated with fluid replacement.
				6 days after administration	The dose of mirogabalin besilate was increased to 5 mg once daily.
				27 days after administration	Serum creatinine worsened from 2.6 to 5.76 mg/dL, and BUN from 32 to 75 mg/dL.
				35 days after administration (day of discontinuation)	The administration of mirogabalin besilate was discontinued.
				2 days after discontinuation	Outcome of renal failure, hepatic function disorder, increased inflammatory reaction, generalised oedema: Resolving

Laboratory test value

	Date unknown	29 days before adminis-tration	3 days after adminis-tration	23 days after adminis-tration	27 days after adminis-tration	34 days after adminis-tration	17 days after discon-tinuation	24 days after discon-tinuation	38 days after discon-tinuation
Body weight (kg)	48	—	—	—	—	—	—	—	—
Serum creatinine (mg/dL)	—	2.39	2.82	2.60	5.76	6.13	4.69	3.70	3.50
BUN (mg/dL)	—	28	43	32	75	88	45	39	51
AST (IU/L)	—	38	57	40	404	173	27	32	24
ALT (IU/L)	—	16	30	14	191	45	10	17	16
ALP (IU/L)	—	14	302	208	1046	866	208	187	184
γ-GTP (IU/L)	—	26	58	35	52	36	17	20	22
CRP (mg/dL)	—	0.5	8.4	6.2	15.9	12.0	3.9	4.6	4.5

Concomitant drugs: None

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 70s	Peripheral neuropathic pain, right renal cell carcinoma, pathological fracture in the left femur (diabetes mellitus)	5 mg for 14 days ↓ 10 mg for 16 days	**Renal impairment** The patient had a history of smoking.	
				Day 1 of administration	The patient complained of numbness and pain in both hands and shoulders at the orthopedic department. Oral administration of mirogabalin besilate (2.5 mg, twice daily) was initiated for peripheral neuropathic pain, right renal cell carcinoma, and pathologic fracture of the subtrochanteric section of left femur.
				14 days after administration	The response to mirogabalin besilate was inadequate, and pain in the lower extremities also occurred. Since oedema of lower limb and pain were noted, the dose of mirogabalin besilate was increased to 5 mg, twice daily.
				15 days after administration	Decreased kidney function was noted.
				28 days after administration	The patient visited the urology department. Oedema of lower limbs worsened, and pain was noted. Therefore, it was decided that the patients be hospitalized from the next day.
				29 days after administration (day of discontinuation)	The patient was admitted to the hospital. The administration of mirogabalin besilate was discontinued. Care for lymphoedema was initiated, and furosemide was administered.
				15 days after discontinuation	Oedama tended to be alleviated. No aggravation of numbness was noted after discontinuation of mirogabalin besilate.
				Date unknown	Outcome of lower leg oedema, decreased kidney function: Resolving Outcome of pain: Unrecovered

Laboratory test value

	7 days before adminis-tration	Before adminis-tration	14 days after adminis-tration	28 days after adminis-tration	29 days after adminis-tration	1 day after discon-tinuation	9 days after discon-tinuation	14 days after discon-tinuation
Body weight (kg)	—	67	—	—	72	—	—	—
Creatinine clearance (mL/min)	—	50	40	30	—	—	—	—
Serum creatinine (mg/dL)	1.22	1.01	1.29	1.77	—	1.31	2.04	1.00
BUN (mg/dL)	26.2	25.2	29.3	44.8	—	34.1	60.4	32.6

Concomitant drugs: Nivolumab (genetical recombination), rebamipide, loxoprofen sodium hydrate

2 Pemafibrate

Brand name (name of company)	Parmodia Tablets 0.1 mg, Parmodia XR Tablets 0.2 mg, 0.4 mg (Kowa Company, Ltd.)
Therapeutic category	Agents for hyperlipidemias
Indications	Hyperlipidaemia (including familial hyperlipidaemia)

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Hepatic impairment, jaundice
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, falling under grade 3 or higher by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 among the cases retrieved by MedDRA ver.27.0 SMQ “Drug related hepatic disorders-comprehensive search” Cases involving hepatic impairment reported in Japan: 9 (including 3 cases accompanied by jaundice) (No patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Parmodia Tablets 0.1 mg: Approximately 560,000 Parmodia XR Tablets 0.2 mg: Approximately 420,000 Parmodia XR Tablets 0.4 mg: Approximately 60,000 Japanese market launch: Tablets: June 2018 XR Tablets: November 2023

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td rowspan="11">1</td><td rowspan="11">Male
50s</td><td rowspan="11">Dyslipidaemia
(hypertension, sleep apnoea syndrome, gastritis)</td><td rowspan="11">0.2 mg
for 74 days</td><td colspan="2">Drug-induced liver injury</td></tr>
<tr><td>Day 1 of administration</td><td>Administration of pemafibrate was initiated.</td></tr>
<tr><td>Day 36 of administration</td><td>Worsened liver function values were noted. However, the patient was followed up until the next visit to the hospital after one month, since it was a slight increase.</td></tr>
<tr><td>Day 72 of administration</td><td>Significant exacerbation of liver function values was noted.</td></tr>
<tr><td>Day 74 of administration (day of discontinuation)</td><td>Administration of pemafibrate was discontinued.</td></tr>
<tr><td>4 days after discontinuation</td><td>Aggravation of liver function was noted also in the re-examination.</td></tr>
<tr><td>Date unknown</td><td>Jaundice was observed.</td></tr>
<tr><td>7 days after discontinuation</td><td>The patient was referred to another hospital and was immediately admitted.</td></tr>
<tr><td>19 days after discontinuation</td><td>Outcome: Resolving.</td></tr>
<tr><td>53 days after discontinuation</td><td>Normalization of liver function values was confirmed.</td></tr>
<tr><td colspan="6">Laboratory test value
<table>
<tr><th></th><th>32 days before administration</th><th>Day 36 of administration</th><th>Day 72 of administration</th><th>4 days after discontinuation</th><th>53 days after discontinuation</th></tr>
<tr><td>AST (IU/L)</td><td>20</td><td>77</td><td>1335</td><td>1704</td><td>18</td></tr>
<tr><td>ALT (IU/L)</td><td>16</td><td>54</td><td>1880</td><td>2550</td><td>12</td></tr>
<tr><td>ALP (IU/L)</td><td>76</td><td>57</td><td>128</td><td>139</td><td>106</td></tr>
<tr><td>γ-GTP (IU/L)</td><td>36</td><td>23</td><td>263</td><td>289</td><td>47</td></tr>
<tr><td>T-Bil (mg/dL)</td><td>—</td><td>—</td><td>3.6</td><td>4.9</td><td>—</td></tr>
</table></td></tr>
<tr><td colspan="6">Concomitant drugs: Amlodipine besilate, candesartan cilexetil, olopatadine hydrochloride, famotidine</td></tr>
</table>

3 Purified pineapple stem juice

Brand name (name of company)	NexoBrid gel 5 g (Kaken Pharmaceutical Co., Ltd.)
Therapeutic category	Other agents for epidermis
Indications	Removal of necrotic tissue of deep dermal burn or deep burn

PRECAUTIONS (Revised language is underlined.)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with wound such as decompression incision and laceration This drug should not be applied to the wound area of a decompression incision, laceration, etc. The wound area which may come into contact with this drug should be protected in advance with petrolatum ointments, petrolatum gauze, etc. Contact between the wound area and this drug may lead to haemorrhage
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Application site haemorrhage Application site haemorrhage may occur, which may lead to haemorrhagic shock.
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 with an adverse reaction name (PT) containing “haemorrhage” Cases involving haemorrhage reported in Japan: 4 (No patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 480 Japanese market launch: August 2023

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/ age</th><th>Reason for use (complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male 20s</td><td>Third degree thermal burn (airway burns)</td><td>30 g 1 day (once)</td><td colspan="2">Haemorrhagic shock</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Time unknown on day of administration</td><td>The patient suffered third degree thermal burn (DB) (area: 50% TBSA, regions: neck, body, upper extremities, thighs).</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Approximately 11 hours before administration</td><td>Escharotomy was performed on the precordium, abdomen, and bilateral upper extremities. The sites of escharotomy and application sites of purified pineapple stem juice overlapped in some parts.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Approximately 8 hours and 30 minutes before administration</td><td>Administration of noradrenaline injection was started.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>From approximately 8 hours before administration to 7 hours before administration</td><td>Surgical debridement was performed. The sites of debridement were different from the application sites of purified pineapple stem juice.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Time unknown</td><td>Before application of purified pineapple stem juice, gauzes soaked in chlorhexidine gluconate solution were applied to the procedure sites and they were fixed with bandages. The wound of releasing incision was protected with a thick application of petroleum ointment.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Time of administration</td><td>Six bottles of purified pineapple stem juice were used for the third degree thermal burn (DB) (area: 15% TBSA, regions: left upper extremity, precordium). After application of purified pineapple stem juice, the skin was covered with film.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Approximately 3 hours after administration</td><td>Although maximum attention was paid to prevent contamination of purified pineapple stem juice to the wound area, it contaminated the exposed blood vessels. Excessive haemorrhage from the cutaneous veins of the left upper extremity and precordium was noted (amount of blood loss: Unknown). Systolic arterial blood pressure decreased to a range between 50 and 59 mmHg.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>4 hours after administration</td><td>After purified pineapple stem juice was left to stand as scheduled, it was removed and bandages were changed. The dose of noradrenaline injection was increased.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Time unknown</td><td>Blood transfusion (human red blood cells 2U×9, fresh frozen plasma transfusion 2U×12, platelet concentrate transfusion 20U×1) and a haemostasis procedure were performed.</td></tr>
<tr><td></td><td></td><td></td><td></td><td>5 hours and 40 minutes after administration</td><td>Haemostasis was completed, and stabilization of the blood pressure was confirmed.</td></tr>
<tr><td></td><td colspan="5">Laboratory test value
<table>
<tr><th></th><th>1 hour before adminis-tration</th><th>At the start of adminis-tration</th><th>1 hour after adminis-tration</th><th>2 hours after adminis-tration</th><th>3 hours after adminis-tration</th><th>3 hours and 10 minutes after adminis-tration</th><th>4 hours after adminis-tration</th><th>4 hours and 23 minutes after adminis-tration</th><th>4 hours and 29 minutes after adminis-tration</th><th>4 hours and 43 minutes after adminis-tration</th></tr>
<tr><td>Systolic arterial blood pressure (mmHg)</td><td>115</td><td>113</td><td>107</td><td>72</td><td>62</td><td>56</td><td>62</td><td>36</td><td>60</td><td>94</td></tr>
</table></td></tr>
<tr><td></td><td colspan="5">Concomitant drugs: Acetated Ringer’s solution, propofol, cefazolin sodium, omeprazole sodium, noradrenaline, fentanyl citrate, physiological saline, midazolam, heparin sodium, ketamine hydrochloride, atropine sulfate hydrate, calcium gluconate hydrate</td></tr>
</table>

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td rowspan="11">2</td><td rowspan="11">Female
80s</td><td rowspan="11">Third degree thermal Burn
(cardiac failure, acute renal failure, dementia)</td><td rowspan="11">30g
1 day (once)</td><td colspan="2">Haemorrhagic shock</td></tr>
<tr><td>26 days before administration</td><td>The patient suffered third degree thermal burn (DB) (area: 17% TBSA, regions: left upper extremity, left foot, left buttock) due to taking a high-temperature bath for a long time.</td></tr>
<tr><td>22 days before administration</td><td>Escharotomy was performed on the left upper extremity, left buttock, and left lower extremity. Debridement and split thickness skin grafts were performed from the dorsum of the left hand to the forearm and on the dorsum of the left foot.</td></tr>
<tr><td>15 days before administration</td><td>Iodine ointment and sucrose/povidone-iodine ointment were started for wound infection control.</td></tr>
<tr><td>13 days before administration</td><td>Debridement and split thickness skin graft were performed on the lower back and buttocks and the left foot.</td></tr>
<tr><td>Time of administration on day of administration</td><td>Six bottles of purified pineapple stem juice were applied for third degree thermal burn (DB) (area: 15% TBSA, regions: left upper extremity, left foot, left buttock).</td></tr>
<tr><td>26 minutes after administration</td><td>A nurse found a DIC-like oozing haemorrhage from all the application sites of purified pineapple stem juice (capillaries on the surface of granulation). Blood pressure decreased to a range between 60 and 69 mmHg, and the dose of noradrenaline intravenous injection was increased to 1.0 mg/h.</td></tr>
<tr><td>30 minutes after administration</td><td>Purified pineapple stem juice was wiped off and washed out, and the application sites were treated with gauze packing. A procedure with a bipolar cautery was performed.</td></tr>
<tr><td>45 minutes after administration</td><td>Haemostasis was completed. The total blood loss was 1,550 g.</td></tr>
<tr><td>Approximately 2 hours and 30 minutes after administration</td><td>Two units of human red blood cells were transfused.</td></tr>
<tr><td>Approximately 3 hours and 30 minutes after administration</td><td>Two units of human red blood cells were transfused.</td></tr>
<tr><td>Unknown time on day of administration</td><td>Haemorrhagic shock resolved.</td></tr>
<tr><td colspan="6">Laboratory test value
<table>
<tr><th></th><th>Approximately 6 hours before administration</th><th>Approximately 4 hours after administration</th><th>Approximately 10 hours and 30 minutes after administration</th><th>1 day after administration</th><th>2 days after administration</th><th>3 days after administration</th><th>4 days after administration</th></tr>
<tr><td>Blood pressure (mmHg)</td><td>105/55</td><td>68/32</td><td>98/52</td><td>118/60</td><td>107/21</td><td>110/49</td><td>107/51</td></tr>
<tr><td>Pulse (/min)</td><td>58</td><td>89</td><td>122</td><td>126</td><td>135</td><td>138</td><td>122</td></tr>
</table></td></tr>
<tr><td colspan="6">Concomitant drugs: Magnesium oxide, elobixibat hydrate, iodine, sucrose/povidone-iodine</td></tr>
</table>

4 [1] Preparations containing sulfamethoxazole sodium
[2] Preparations containing sulfamethoxazole

Brand name (name of company)	[1] Rohto Antibacterial Eye Drops i (Rohto Pharmaceutical Co., Ltd.) and the other OTC drugs [2] Sante Medical Antibacterial (Santen Pharmaceutical Co., Ltd.) and the other OTC drugs
Therapeutic category	Agents for ophthalmic use
Indications	Hordeolum, conjunctivitis (epidemic conjunctivitis), eye itching, blepharitis (erosion of eyelid)

PRECAUTIONS (Revised language is underlined.)

When not to use the product (If the patient does not follow the instructions, the current symptoms may be aggravated, or adverse reactions may occur.) (newly added)

This drug product should not be used in the following persons:
Persons who have had an allergic symptom to this product or ingredients of this product

Consultation (newly added)

The following serious symptoms may occur rarely. In such a case, medical attention should be sought immediately.

Name of symptoms	Symptoms
Shock (anaphylaxis)	Symptoms such as itching of skin, urticaria, hoarseness, sneezing, itchy throat, breathing difficulties, palpitations, and clouding of consciousness may occur immediately after use.

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 anaphylaxis reported in Japan: 4 (No patient mortality)
Number of patients using the drug as estimated by the MAH during the previous 1-year period:
Rohto Antibacterial Eye Drops i: Approximately 1,200,000
Sante Medical Antibacterial: Approximately 450,000
Japanese market launch: -

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 40s	Conjunctivitis	Unknown for 1 day	**Anaphylaxis**	
				Day 1 of administration (day of onset) (day of discontinuation)	The patient self-diagnosed herself with conjunctivitis. She instilled several drops of the drug (sulfamethoxazole sodium, dipotassium glycyrrhizinate, ε-aminocaproic acid). Following this, itching occurred around the eyes, and her entire face became red and swollen. Due to dyspnoea and a decreased level of consciousness, she called an ambulance and visited the emergency department. At the visit, SpO_2 was 98%, BP 105/45 mmHg, and BT 36.5°C. She was diagnosed with anaphylaxis. Famotidine 20 mg, polaramine 5 mg, and dexamethasone sodium phosphate 6.6 mg were administered by drip infusion. Since the symptoms improved, she returned home. After that, this drug (sulfamethoxazole sodium, dipotassium glycyrrhizinate, ε-aminocaproic acid) was not used. The symptoms did not relapse.
				55 days after discontinuation	The result of a prick test (The ophthalmic solution was diluted with saline at 1:1000.) was positive.
				144 days after discontinuation	The prick test was performed with each of the 3 main ingredients of the ophthalmic solution (sulfamethoxazole sodium, dipotassium glycyrrhizinate, ε-aminocaproic acid) diluted at 1:1000 of the used concentration. The result was positive only for sulfamethoxazole sodium.

4

Revisions of PRECAUTIONS (No. 353)

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 27, 2024.

1 Antiepileptics, psychotropic agents
Sodium valproate

Brand name	Depakene Tablets 100 mg, 200 mg, Depakene R Tablets 100 mg, 200 mg, Depakene Fine Granules 20%, 40%, Depakene Syrup 5% (Kyowa Kirin Co., Ltd.), Selenica-R Granules 40%, Selenica-R Tablets 200 mg, 400 mg (Kowa Company, Ltd.), and the others
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Uses (newly added)**	There has been an observational study performed in Scandinavian countries which suggests that infants/children with paternal exposure to sodium valproate within 3 months prior to conception had an increased risk of neurodevelopmental disorder compared with those with paternal exposure to lamotrigine or levetiracetam (adjusted hazard ratio 1.50 [95% confidence interval: 1.09−2.07]), although the causal relationship to sodium valproate is unclear. On the other hand, there has been an overseas observational study in fathers with epilepsy which showed that infants/children with paternal exposure to sodium valproate within 120 days prior to conception did not have a statistically significant increased risk of neurodevelopmental disorder compared with those with no paternal exposure to sodium valproate.

2 Other agents affecting central nervous system
Mirogabalin besilate

Brand name	Tarlige Tablets 2.5 mg, 5 mg, 10 mg, 15 mg, Talige OD Tablets 2.5 mg, 5 mg, 10 mg, 15 mg (Daiichi Sankyo Co., Ltd.)
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Renal impairment

3 Antihypertensives
Azelnidipine

Brand name	Calblock Tablets 8 mg, 16 mg (Daiichi Sankyo Co., Ltd.), and the others
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	Patients receiving the following drugs: Itraconazole, miconazole (oral dosage form, injections), fluconazole, fosfluconazole, voriconazole, posaconazole, HIV protease inhibitors (preparations containing ritonavir, nelfinavir, atazanavir, fosamprenavir, preparations containing darunavir), preparations containing cobicistat

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
The following azoles Itraconazole, miconazole (oral dosage form, injections), fluconazole, fosfluconazole, voriconazole, posaconazole	Co-administration of azelnidipine 8 mg with itraconazole 50 mg[note)] has been reported to result in a 2.8-fold increase in the AUC of azelnidipine.	It is considered that these drugs inhibit CYP3A4 and that the clearance of azelnidipine is decreased.

Note) This is based on the results of a co-administration study with low-dose itraconazole. Refer to the electronic package insert of itraconazole for the dose of itraconazole.

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Azoles (excluding drugs which are contraindicated for co-administration) Fosravuconazole, etc.	The effect of azelnidipine may be enhanced. If necessary, azelnidipine should be reduced in dosage or discontinued, or the administration of these drugs should be discontinued.	It is considered that these drugs inhibit CYP3A4 and that the clearance of azelnidipine is decreased.

4 Antihypertensives

Olmesartan medoxomil/azelnidipine

Brand name Rezaltas Combination Tablets LD, HD (Daiichi Sankyo Co., Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) Patients receiving the following drugs: Itraconazole, miconazole (oral dosage form, injections), fluconazole, fosfluconazole, voriconazole, posaconazole, HIV protease inhibitors (preparations containing ritonavir, nelfinavir, atazanavir, fosamprenavir, preparations containing darunavir), preparations containing cobicistat

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

Drugs	Signs, symptoms, and treatment	Mechanism /risk factors
The following azoles: Itraconazole, miconazole (oral dosage form or injections), fluconazole, fosfluconazole, voriconazole, posaconazole	Co-administration of azelnidipine 8 mg with itraconazole 50 mg[note)] has been reported to result in a 2.8-fold increase in the AUC of azelnidipine.	It is considered that these drugs inhibit CYP3A4 and that the clearance of azelnidipine is decreased.

Note) This is based on the results of a co-administration study with low-dose itraconazole. Refer to the electronic package insert of itraconazole for the dose of itraconazole.

10.2 Precautions for Co-Administration (This

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors

drug should be administered with caution when co-administered with the following.) (newly added)	Azoles (excluding drugs which are contraindicated for co-administration) Fosravuconazole, etc.	The effect of azelnidipine may be enhanced. If necessary, the prescription should be switched to the one in which azelnidipine, which is the ingredient of this drug, is reduced in dosage or discontinued, or the administration of these drugs should be discontinued.	It is considered that these drugs inhibit CYP3A4 and that the clearance of azelnidipine is decreased.

5 Agents for hyperlipidemias

Pemafibrate

Brand name	Parmodia Tablets 0.1 mg, Parmodia XR Tablets 0.2 mg, 0.4 mg (Kowa Company, Ltd.)
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Hepatic impairment, jaundice

6 Other agents for epidermis

Purified pineapple stem juice

Brand name	NexoBrid gel 5 g (Kaken Pharmaceutical Co., Ltd.)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with wound such as decompression incision and laceration This drug should not be applied to the wound area of a decompression incision, laceration, etc. The wound area which may come into contact with this drug should be protected in advance with petrolatum ointments, petrolatum gauze, etc. Contact between the wound area and this drug may lead to haemorrhage.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Application site haemorrhage Application site haemorrhage may occur, which may lead to haemorrhagic shock

7 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, azelnidipine, olmesartan medoxomil/azelnidipine, 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
Azelnidipine Olmesartan medoxomil/ azelnidipine	The effect of azelnidipine may be enhanced.	The plasma concentration of azelnidipine is expected to rise due to the inhibition of CYP3A4 by co-administration with posaconazole.

8 Other chemotherapeutics

Fosravuconazole L-lysine ethanolate

Brand name

Nailin Capsules 100 mg (Sato Pharmaceutical Co., Ltd.)

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

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs metabolized mainly by CYP3A Simvastatin Midazolam Azelnidipine etc.	Fosravuconazole L-lysine ethanolate may increase the blood concentration of these drugs.	The metabolism of these drugs is suppressed by the inhibitory activities of ravuconazole against CYP3A.

9 X-ray contrast agents

Iodixanol

Brand name

Visipaque 270 Injection 20 mL, 50 mL, 100 mL, Visipaque 320 Injection 50 mL, 100 mL (GE Healthcare Pharma Co., Ltd.)

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions
<Common to all indications>
(newly added)

Acute generalised exanthematous pustulosis

10 Agents for ophthalmic use

[1] Preparations containing sulfamethoxazole sodium (OTC antibacterial ophthalmic solution)
[2] Preparations containing sulfamethoxazole (OTC antibacterial ophthalmic solution)

Brand name

[1] Rohto Antibacterial Eye Drops i (Rohto Pharmaceutical Co., Ltd.) and the other OTC drugs
[2] Sante Medical Antibacterial (Santen Pharmaceutical Co., Ltd.) and the other OTC drugs

When not to use the product
(If the patient does not follow the instructions, the current symptoms may be aggravated, or adverse reactions may occur.)
(newly added)

This drug product should not be used in the following persons:
Persons who have had an allergic symptom to this product or ingredients of this product

Consultation
If the following symptoms are observed after using this drug, these may be adverse reactions. In such cases, the use of this drug should be immediately discontinued, and a physician, pharmacist or registered salesclerk should be consulted presenting them with this document.
(newly added)

The following serious symptoms may occur rarely. In such a case, medical attention should be sought immediately.

Name of symptoms	Symptoms
Shock (anaphylaxis)	Symptoms such as itching of skin, urticaria, hoarseness, sneezing, itchy throat, breathing difficulties, palpitations, and clouding of consciousness may occur immediately after use.

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

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiatation
◎	Pneumococcal 20-valent conjugate vaccine adsorbed (mutated diphtheria CRM_{197} conjugate)[*1] Prevenar 20 Suspension Liquid for Injection	Pfizer Japan Inc.	August 30, 2024
◎	Brivaracetam Briviact Tablets 25 mg, 50 mg, Briviact for I.V. injection 25 mg	UCB Japan Co. Ltd.	August 30, 2024
◎	Mepolizumab (genetical recombination)[*2] Nucala solution for s.c. injection 100 mg	GlaxoSmithKline K.K.	August 28, 2024
◎	Maribavir Livtencity tablets 200 mg	Takeda Pharmaceutical Company Limited	August 28, 2024
◎	Vilanterol trifenatate/fluticasone furoate Relvar 50 Ellipta 14 doses for Pediatric, Relvar 50 Ellipta 30 doses for Pediatric	GlaxoSmithKline K.K.	August 23, 2024
◎	Pirtobrutinib Jaypirca Tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	August 21, 2024
◎	Zinc histidine hydrate Zintus Tablets 50 mg	Nobelpharma Co., Ltd.	August 20, 2024
◎	Momelotinib hydrochloride hydrate Omjjara Tablets 100 mg, 150 mg, 200 mg	GlaxoSmithKline K.K.	August 15, 2024
◎	Iptacopan hydrochloride hydrate Fabhalta capsules 200 mg	Novartis Pharma K.K.	August 15, 2024
◎	Favipiravir[*3] Avigan Tablets 200 mg	FUJIFILM Toyama Chemical Co., Ltd.	August 15, 2024
◎	Sargramostim (genetical recombination) Sargmalin for inhalation 250 μg	Nobelpharma Co., Ltd.	July 29, 2024
◎	Fluciclovine (^{18}F) Injection Axumin Injection	Nihon Medi-Physics Co., Ltd.	July 2, 2024
	Concizumab (genetical recombination)[*4] Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	June 24, 2024

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.

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiatation
Vilanterol trifenatate/fluticasone furoate Relvar 100 Ellipta 14 doses, 30 doses	GlaxoSmithKline K.K.	June 24, 2024
Baricitinib[*5] Olumiant tablets 1 mg	Eli Lilly Japan K.K.	June 17, 2024
Zolbetuximab (genetical recombination) Vyloy for I.V. infusion 100 mg	Astellas Pharma Inc.	June 12, 2024
Nemolizumab (genetical recombination)[*6] Mitchga Vials 30 mg	Maruho Co., Ltd.	June 11, 2024
Susoctocog alfa (genetical recombination) Obizur Intravenous Injection 500	Takeda Pharmaceutical Company Limited	June 10, 2024
Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 10 mg Syringe	AstraZeneca K.K.	June 3, 2024
Recombinant respiratory syncytial virus vaccine[*7] 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
Sacubitril valsartan sodium hydrate[*8] Entresto Granules for Pediatric 12.5 mg, 31.25 mg	Novartis Pharma K.K.	May 22, 2024
Luspatercept (genetical recombination)	Bristol-Myers Squibb	May 20,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiatation
	Reblozyl for S.C. injection 25 mg, 75 mg	K.K.	2024
	Letermovir[*9] Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 17, 2024
	Talazoparib tosilate Talzenna capsules 0.1 mg, 0.25 mg, 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[*10] Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	March 26, 2024
	Efgartigimod alfa (genetical recombination)[*11] Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	March 26, 2024
	Baricitinib[*12] Olumiant tablets 2 mg, 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-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Quintovac Aqueous Suspension Injection	KM Biologics Co., Ltd.	March 14, 2024

*1 Prophylaxis of pneumococcal disease (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V,10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) in the elderly and individuals who are considered to be at high risk of pneumococcal disease

*2 Chronic sinusitis with nasal polyps (for use only in patients who have not sufficiently responded to conventional treatments)

*3 Severe fever with thrombocytopenia syndrome virus infection

*4 Prevention of bleeding tendency in patients with congenital haemophilia who don't have inhibitors against blood coagulation factor VIII or IX

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

*6 Addition of a pediatric dosage indicated for the following diseases in patients who have not responded sufficiently to conventional treatments.
Pruritus associated with atopic dermatitis
Prurigo nodularis

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

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

*9 Prophylaxis of cytomegalovirus infections in organ transplant recipients

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

*11 Chronic idiopathic thrombocytopenic purpura

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