Pharmaceuticals and Medical Devices Safety Information

No. 408 March 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/) and on the MHLW website (https://www.mhlw.go.jp/, only available in Japanese language).

Available information is listed here

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

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

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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 408 March 2024

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Preparation of Materials for Information Provision in Cooperation With the Patients' Associations (Activities by the PMDA)**		The PMDA provides information on the safety of drugs through its web site, the Medi-navi service, etc. This section introduces the activities on a trial basis by the Japanese Lysosome Disease Patients and Family Association (hereinafter referred to as "J-LSDA") and the PMDA, aiming to overcome challenges concerning proper information provision to patients and efficient information collection.	4
2	**Revision of PRECAUTIONS for Topiramate**	*P*	Topiramate is the drug indicated for "concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizures) in epileptic patients who are not sufficiently responsive to other antiepileptic drugs," and the marketing of topiramate was initiated in September 2007. As a result of investigation including the opinions of experts regarding the possible occurrence of neurodevelopmental disorder in infants/children born to topiramate-exposed mothers during pregnancy, the MHLW considered it necessary to take safety measures, and issued a notification instructing the marketing authorization holders (MAHs) to revise PRECAUTIONS on February 15, 2024. This section will introduce the details of the review.	6
3	**Revision of PRECAUTIONS (No. 348)**	*P*	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine (and 5 others)	8
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of January 31, 2024	11

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 only available in Japanese.)

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

Abbreviations

ADR	Adverse Drug Reaction
aHRs	Adjusted Hazard Ratios
EPPV	Early Post-marketing Phase Vigilance
J-LSDA	Japanese Lysosome Disease Patients and Family Association
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division

1
Preparation of Materials for Information Provision in Cooperation With the Patients' Associations (Activities by the PMDA)

1. Introduction

The PMDA provides information on the safety of drugs through its web site, the Medi-navi service, etc. To reliably provide information to patients who use drugs is an issue to be tackled. With respect to collection of safety information as well, the majority of adverse reactions are reported by pharmaceutical companies or medical professionals. To utilize reports also from patients for safety measures is a future challenge.

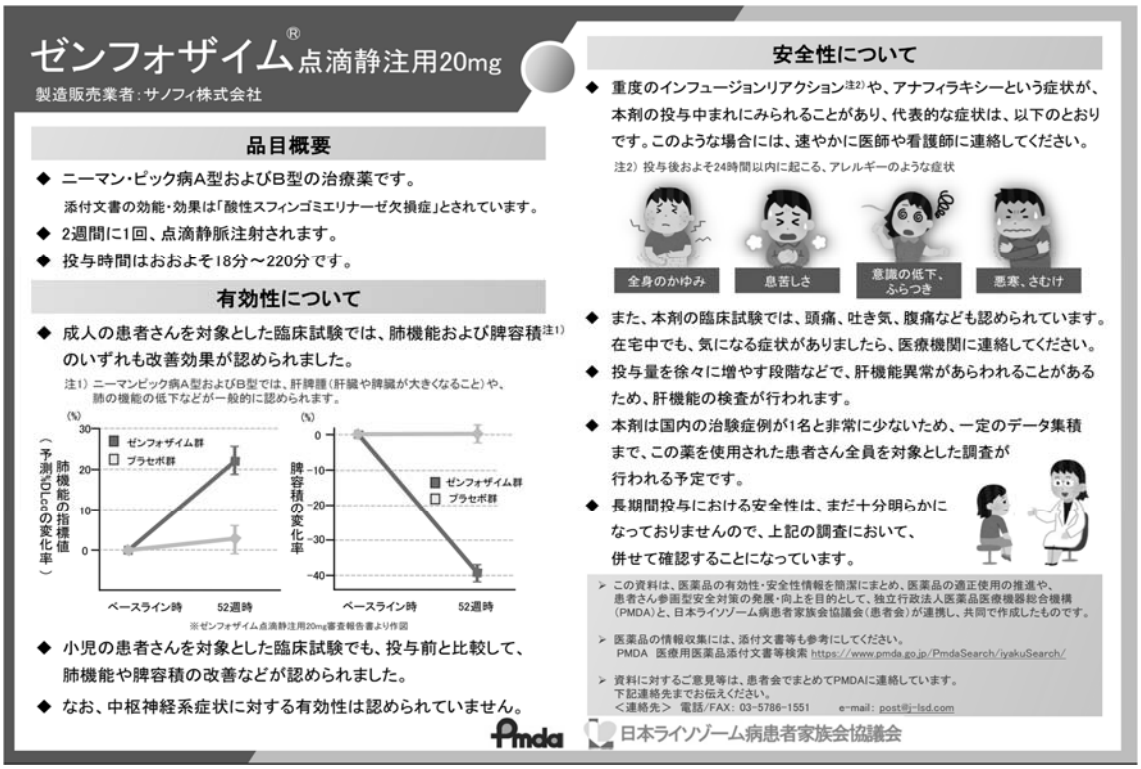
This section introduces the activities on a trial basis by the Japanese Lysosome Disease Patients and Family Association (hereinafter referred to as "J-LSDA") and the PMDA, aiming to overcome challenges concerning proper information provision to patients and efficient information collection.

2. Outline of activities

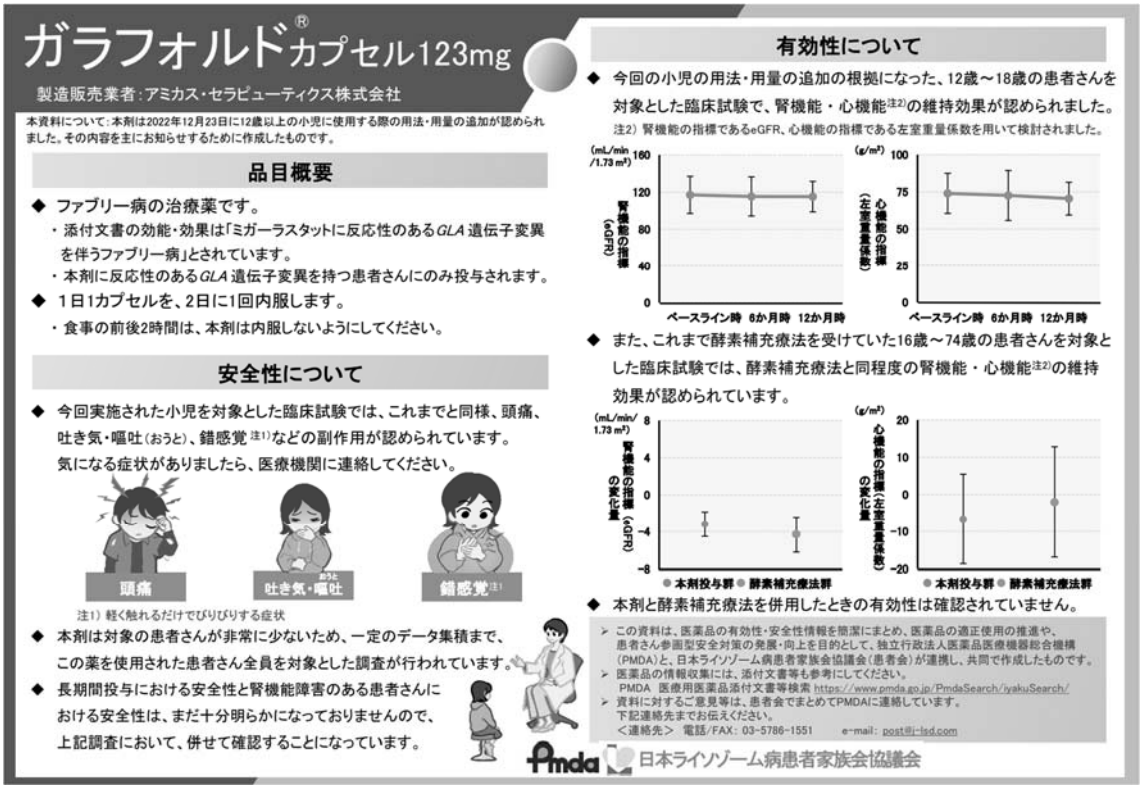
As part of the cooperation between the J-LSDA and PMDA, easy-to-understand materials providing information on the efficacy and safety of newly approved drugs, etc. were prepared. These materials have been published on the websites of the J-LSDA and PMDA (only in Japanese).

In addition, information on Revisions of PRECAUTIONS, etc. for drugs related to the J-LSDA was provided in a timely manner.

Xenpozyme for I.V. Infusion 20 mg (Sanofi K.K.)



Galafold Capsules 123 mg (Amicus Therapeutics, Inc.)



3. Closing remark

The PMDA continues to promote the proper use of drugs through such activities as preparation of materials in cooperation with patients' associations. Healthcare professionals are requested to properly provide information to patients and to cooperate with collection of information on adverse drug reactions, etc. from patients.

[References]
• Activities related to cooperation with patients' associations
https://www.pmda.go.jp/safety/0004.html (only in Japanese)

2

Revision of PRECAUTIONS for Topiramate

1. Introduction

Topiramate is the drug indicated for “concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizures) in epileptic patients who are not sufficiently responsive to other antiepileptic drugs,” and the marketing of topiramate was initiated in September 2007.

As a result of the investigation including the opinions of experts regarding the possible occurrence of neurodevelopmental disorder in infants/children born to topiramate-exposed mothers during pregnancy, the MHLW considered it necessary to take safety measures, and issued a notification instructing the marketing authorization holders (MAHs) to revise PRECAUTIONS on February 15, 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 package insert to add a precaution for the risk of neurodevelopmental disorder in infants/children born to topiramate-exposed mothers on the basis of the epidemiological literature.

In response to the publication of overseas epidemiological literature, the MAHs of topiramate in Japan requested a consultation concerning revision of the package insert to add the risk of neurodevelopmental disorder in order to alert healthcare professionals.

On the basis of the overseas epidemiological literature, the necessity of revising the electronic package insert in Japan including the precautions not only for women during pregnancy but also for those of child-bearing potential was discussed.

3. Details of the review

The overseas epidemiological literature concerning the risk of neurodevelopmental disorder in infants/children born to topiramate-exposed mothers during pregnancy was assessed. As a result, it was considered that the possible occurrence of neurodevelopmental disorder in infants/children born to topiramate-exposed mothers during pregnancy was suggested from the results of the following 2 articles.

- In the cohort study using health register and social register data in 5 Scandinavian countries, the accumulated rates of incidence and the adjusted hazard ratios (aHRs) of autism spectrum disorder, intellectual development disorder, and neurodevelopmental disorder were calculated for children at the age of 8 whose mothers were prescribed antiepileptic drugs at least once between the date of the last menstrual period and the delivery date (exposed children) and for those whose mothers were not prescribed antiepileptic drugs between 90 days prior to the last menstrual period and the delivery date (unexposed children). Compared to the unexposed children born to mothers with epilepsy, the aHRs for autism spectrum disorder, intellectual development disorder, and neurodevelopmental disorder in children exposed to topiramate alone were 2.8 (95% CI; 1.4−5.7), 3.5 (95% CI; 1.4−8.6), and 2.1 (95% CI; 1.1−4.0), respectively.[1)]
- In another cohort study using health register and social register data in 5 Scandinavian countries, diagnoses of psychiatric disorders in infants/children born to mothers who were prescribed antiepileptic drugs at least once between 30 days prior to the date of the last menstrual period and the delivery date (exposed infants/children) and those whose mothers were not prescribed antiepileptic drugs (unexposed infants/children) were investigated. Compared to the unexposed infants/children born to mothers with epilepsy, the aHRs of

infants/children exposed to topiramate alone were 2.38 (95%CI; 1.40−4.06) for attention deficit hyperactivity disorder, 2.23 (95%CI; 0.90−5.50) for intellectual development disorder, and 1.93 (95%CI; 0.95−3.94) for autism spectrum disorder.[2)]

In addition to the inclusion of the risk to “PRECAUTIONS,” it was decided that patients should be fully informed of the risks that may occur in infants/children born to topiramate-exposed mothers when topiramate is used in women of child-bearing potential, pregnant women, or women who may be pregnant.

4. Closing remark

It is considered that pregnant women or women who may be pregnant are administered topiramate after it is decided that the potential therapeutic benefits (prevention of frequent epileptic seizures in mothers and protection of foetuses from hypoxia) are considered to outweigh the potential risks taking into account the risk of teratogenicity. In addition, healthcare professionals are requested to fully inform the patients of the risks regarding the occurrence of neurodevelopmental disorder, which was newly added to the PRECAUTIONS. Similarly, women of child-bearing potential should be fully informed of the risks of this drug concerning the teratogenicity and the occurrence of neurodevelopmental disorder.

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 would be appreciated.

[References]
1) Bjørk MH, et al.:JAMA Neurol. 2022;79:672-681.
2) Dreier JW, et al.:JAMA Neurol. 2023;80:568-577.

[Reference information]
•Revisions of PRECAUTIONS (PSB/PSD Notification No.0215-1 dated February 15, 2024)
https://www.mhlw.go.jp/content/001210404.pdf (in Japanese)
English translation by the PMDA (February 15, 2024)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0011.html

3
Revision of PRECAUTIONS (No.348)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated February 6, February 15, 2024.

1 Mixed biological preparations
Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine (Gobik Aqueous Suspension Syringes)

Brand name	Gobik Aqueous Suspension Syringes (Mitsubishi Tanabe Pharma Corporation)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Individuals who receive vaccinations and timings of vaccinations This vaccine should be administered to individuals aged 2 months to 90 months after birth. The initial immunization should be started at the ages of 2 months or over and under 7 months after birth, and the vaccine should be administered at intervals of 20 to 56 days as the standard practice. The booster dose should be given between 6 months to 18 months after the end date of the vaccinee's initial immunization as the standard practice.

2 Mixed biological preparations
Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine (Quintovac Aqueous Suspension Injection)

Brand name	Quintovac Aqueous Suspension Injection (Meiji Seika Pharma Co., Ltd.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Individuals who receive vaccinations and timings of vaccinations This vaccine should be administered to individuals aged 2 months to 90 months after birth. The initial immunization should be started at the ages of 2 months or over and under 7 months after birth, and the vaccine should be administered at intervals of 20 to 56 days as the standard practice. The booster dose should be given between 6 months to 18 months after the end date of the vaccinee's initial immunization as the standard practice.

3 Antiepileptics
Topiramate

Brand name	Topina Tablets 25 mg, 50 mg, 100 mg, Topina Fine Granules 10% (Kyowa Kirin Co., Ltd.), and the others
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.4 Patients with Reproductive Potential**	When this drug is used in women of child-bearing potential, the patients should be fully informed of the risks that may occur in infants/children born to topiramate-exposed mothers.

(newly added)	
9.5 Pregnant Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits (prevention of frequent epileptic seizures in mothers and protection of foetuses from hypoxia) are considered to outweigh the potential risks. When this drug is used during pregnancy, or when the women become pregnant while on treatment with this drug, the patients should be fully informed of the risks that may occur in infants/children born to topiramate-exposed mothers. It has been reported as follows. A possible relationship between the infants/children born to topiramate-exposed mothers and the occurrence of neurodevelopmental disorder (autism spectrum disorder, intellectual development disorder, and attention deficit hyperactivity disorder) has been reported in the observational studies performed overseas.

4 Agents affecting metabolism, n.e.c. (not elsewhere classified), other antitumor agents

[1] Nintedanib ethanesulfonate
[2] Axitinib
[3] Aflibercept beta (genetical recombination)
[4] Cabozantinib malate
[5] Sunitinib malate
[6] Sorafenib tosilate
[7] Pazopanib hydrochloride
[8] Vandetanib
[9] Ponatinib hydrochloride
[10] Ramucirumab (genetical recombination)
[11] Regorafenib hydrate
[12] Lenvatinib mesilate

Brand name	[1] Ofev Capsules 100 mg, 150 mg (Nippon Boehringer Ingelheim Co., Ltd.) [2] Inlyta Tablets 1 mg, 5 mg (Pfizer Japan Inc.) [3] Zaltrap 100 mg I.V. Infusion, 200 mg I.V. Infusion (Sanofi K.K.) [4] Cabometyx tablets 20 mg, 60 mg (Takeda Pharmaceutical Company Limited) [5] Sutent Capsule 12.5 mg (Pfizer Japan Inc.) [6] Nexavar tablets 200 mg (Bayer Yakuhin, Ltd.) [7] Votrient Tablets 200 mg (Novartis Pharma K.K.) [8] Caprelsa Tablets 100 mg (Sanofi K.K.) [9] Iclusig tablets 15 mg (Otsuka Pharmaceutical Co., Ltd.) [10] Cyramza Intravenous Injection 100 mg, 500 mg (Eli Lilly Japan K.K.) [11] Stivarga tablets 40 mg (Bayer Yakuhin, Ltd.) [12] Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.)
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Artery dissection Artery dissection including aortic dissection may occur.

5 **Synthetic antibacterials**

Linezolid

Brand name	Zyvox Tablets 600 mg, Zyvox Injection 600 mg (Pfizer Japan Inc.), and the others
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored. If myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, increased urine myoglobin, etc. occur, administration of this drug should be discontinued and appropriate measures should be taken. In addition, patients should be carefully monitored for signs of acute kidney injury due to rhabdomyolysis.
[Under new instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Rhabdomyolysis If myalgia, feelings of weakness, increased CK, increased blood myoglobin, increased urine myoglobin, etc. occur, administration of this drug should be discontinued and appropriate measures should be taken. In addition, patients should be carefully monitored for signs of acute kidney injury due to rhabdomyolysis.

6 Other chemotherapeutics

Itraconazole

Brand name	[1] Itrizole Capsules 50 (Janssen Pharmaceutical K.K.), and the others [2] Itrizole Oral Solution 1% (Janssen Pharmaceutical K.K.), and the others
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Pseudoaldosteronism: Hypokalaemia, increased blood pressure, retention of sodium/body fluid, oedema, increased weight, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Pseudoaldosteronism Hypokalaemia, increased blood pressure, retention of sodium/body fluid, oedema, increased weight, etc. may occur.

4

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of January 31, 2024)
◎: Products for which EPPV was initiated after January 1, 2024

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	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) [*1] 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[*2] 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
	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[*3] Daichirona for Intramuscular Injection	Daiichi Sankyo Co., Ltd.	December 1, 2023
	Rozanolixizumab (genetical recombination) Rystiggo for S.C. Injection 280 mg	UCB Japan Co. Ltd.	November 28, 2023
	Rivaroxaban[*4]		November 24,

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
[1] Xarelto tablets 10 mg, [2] Xarelto fine granules 10 mg, [3] Xarelto OD tablets 10 mg, [4] Xarelto dry syrup for pediatric 51.7 mg, [5] Xarelto dry syrup for pediatric 103.4 mg, [6] Xarelto tablets 2.5 mg	Bayer Yakuhin, Ltd.	2023
Epcoritamab (genetical recombination) Epkinly Subcutaneous Injection 4 mg, 48 mg	Genmab K.K.	November 22, 2023
Efanesoctocog alfa (genetical recombination) Altuviiio Intravenous 250, 500, 1000, 2000, 3000, 4000	Sanofi K.K.	November 22, 2023
Inclisiran sodium Leqvio for s.c. injection syringe 300 mg	Novartis Pharma K.K.	November 22, 2023
Pertuzumab (genetical recombination)/ trastuzumab (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Phesgo Combination for Subcutaneous Injection MA, Phesgo Combination for Subcutaneous Injection IN	Chugai Pharmaceutical Co., Ltd.	November 22, 2023
Coronavirus (SARS-CoV-2) RNA vaccine Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	November 1, 2023
Pegaspargase Oncaspar I.V. Infusion 3750	Nihon Servier Co. Ltd.	October 2, 2023
Ritlecitinib tosilate Litfulo Capsules 50 mg	Pfizer Japan Inc.	September 27, 2023
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	September 26, 2023
Tralokinumab (genetical recombination) Adtralza S.C. Injection 150 mg Syringe	LEO Pharma K.K.	September 26, 2023
Dupilumab (genetical recombination) [1] Dupixent S.C. Injection 200 mg Syringe, [2] Dupixent S.C. Injection 300 mg Syringe, [3] Dupixent S.C. Injection 300 mg Pen	Sanofi K.K.	September 25, 2023
Lenacapavir sodium Sunlenca Subcutaneous Injection 463.5 mg, Sunlenca Tablets 300 mg	Gilead Sciences K.K.	September 13, 2023
Futibatinib Lytgobi tablets 4 mg	TAIHO Pharmaceutical Co., Ltd.	September 7, 2023
Pegcetacoplan Empaveli for Subcutaneous Injection 1080 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	September 4, 2023
Eculizumab (genetical recombination) Soliris for Intravenous Infusion 300 mg	Alexion Pharma Godo Kaisha	August 23, 2023
Ruxolitinib phosphate[*5]	Novartis Pharma K.K.	August 23,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Jakavi Tablets 5 mg, 10 mg		2023
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	August 2, 2023
	Purified pineapple stem juice NexoBrid gel 5 g	Kaken Pharmaceutical Co., Ltd.	August 1, 2023

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

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

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

*4 Prevention of thrombus/embolization formation in patients who have undergone the Fontan procedure

*5 Graft-versus-host disease after haematopoietic stem cell transplant (when steroids are not sufficiently effective)