Pharmaceuticals and Medical Devices Safety Information

No. 419 May 2025

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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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Pharmaceutical Safety Division,
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1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
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No. 419 May 2025

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

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Abbreviations

ALS	Amyotrophic Lateral Sclerosis
ADR	Adverse Drug Reaction
eGFR	Estimated Glomerular Filtration Rate
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
JSHP	Japanese Society of Hospital Pharmacists
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MRONJ	Medication-related Osteonecrosis/osteomyelitis of the Jaws
NSAIDs	Non-steroidal Anti-inflammatory Drug
PMDA	Pharmaceuticals and Medical Devices Agency

1

The Manuals for Management of Individual Serious Adverse Drug Reactions

1. Introduction

Conventional safety measures implemented in Japan had been drug-oriented and mainly “alert-issue” and “post-event response” types, i.e., information on adverse drug reactions (ADRs) was collected and evaluated for each drug and notified to the clinical settings. However, these types of measures may not occasionally be effective enough for early detection of ADRs, leading to serious conditions, for example, for the following reasons:
(1) ADRs may occur in organs that clinicians are not specialized in.
(2) The incidence of serious ADRs is generally low, and some clinicians may have little experience with such events.

Therefore, the MHLW has implemented the “Project of Comprehensive Measures for Serious ADRs” (hereinafter referred to as the "Project," the Project has been ongoing as the “Development Project of the Manuals for Management of Individual Serious ADRs” since FY 2021) since 2005 in order to develop safety measures that “predict” and “prevent” ADRs, focusing on diseases caused by the use of drugs, in addition to conventional drug-oriented ADR safety measures, and to promote research to elucidate the mechanism of ADRs, etc.

In this project, “The Manuals for Management of Individual Serious ADRs” (hereinafter referred to as the "Manuals") were compiled from FY 2005 to FY 2010 by the Committee on the Comprehensive Actions for Serious ADRs who reviewed and compiled the drafts prepared by the Manual preparation committees organized in related academic societies through discussion with the Japanese Society of Hospital Pharmacists (JSHP), which was entrusted by the MHLW in this project. The drafts were prepared with reference to academic papers, various guidelines, health and labour science research project reports, PMDA health and welfare service reports, etc.

In order to promote further utilization of the Manuals after a certain period of time had elapsed since their compilation, revisions based on the latest knowledge have been made over the five years since FY 2016, with the cooperation of related academic societies and others. In addition, we continue to revise the Manuals and prepare new ones as necessary, and promote them to the general public.

2. Progress of revisions, etc.

In FY 2023, we revised the following Manuals. The revisions were reported and discussed at the meeting of the Committee on the Comprehensive Actions for Serious ADRs held on October 17, 2024 and were published in March 2025.

Author	Manual title	Category: New (newly prepared) or Revision
Japanese Society of Oral and Maxillofacial Surgeons	Medication-related osteonecrosis/osteomyelitis of the jaws (MRONJ)	Revision
Japanese Society of Nephrology	Nephrotic syndrome	Revision
	Renal vasculitis (including cases related to antineutrophil cytoplasmic antibody-associated angiitis)	Revision

The Manuals published this time, following those published last year, include explanations about relief for sufferers of ADRs at the end of the “About this Manual” section, which appears at the beginning of each Manual. The Manuals also provide the number of payments for relief benefits in the past 5 years under the Relief System for ADRs and information concerning the Relief System for ADRs at the end of each Manual.

3. Plans for further revisions, etc.

In FY 2024, draft revisions of the following Manuals are being prepared based on the opinions of the Committee and the academic societies. The Manuals are scheduled to be published after being reported and discussed at the Committee on the Comprehensive Actions for Serious ADRs.

Author	Manual title	Category: New (newly prepared) or Revision
Japanese Society of Allergology	Anaphylaxis	Revision
	Angioedema (not induced by non-steroidal anti-inflammatory drugs)	Revision
	Non-steroidal anti-inflammatory drug (NSAIDs, antipyretic analgesics)-induced urticaria/angioedema	Revision
The Japanese Respiratory Society	Interstitial pneumonia	Revision
Japanese Ophthalmological Society	Glaucoma	Revision
	Corneal opacity	Revision

4. Increasing awareness of the Manuals

In order to further disseminate the Manuals and to promote early detection and treatment of serious ADRs, we have been working on awareness-raising initiatives of the Manuals since FY 2021.

In March 2025, we prepared a poster introducing the Manual on “hyperglycemia” and “hypoglycemia” which was revised in December 2023. The electronic version of the poster can be found on the MHLW and PMDA websites:

MHLW https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html (only in Japanese)

PMDA https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html (only in Japanese)

An educational video, etc. for patients and their families about the Manuals that have been prepared and published is also available via the link above. You are encouraged to watch the video.

―― 重篤副作用疾患別対応マニュアル ――

高血糖と低血糖のマニュアルが改訂されました！

高血糖対応マニュアル 初期症状の例

口渇（のどがかわく）、
多飲、多尿、体重減少
など。

口渇

低血糖対応マニュアル 初期症状の例

冷や汗、手足の震え、
急な強い空腹感、
頭痛、動悸など。

冷や汗がでる　急な強い空腹感

- 低血糖はインスリン製剤のみでなく、SU薬等の経口薬でも起きやすい。
- 糖尿病治療薬以外により低血糖が起こることがある（抗不整脈薬、抗菌薬等）。
- 薬剤によって高血糖が起こることがある（ステロイド薬、免疫チェックポイント阻害薬による1型糖尿病発症時等）。

患者さん自身が初期症状に気づけるように、
マニュアルを利用して具体的に説明し支援しましょう。
家族、医療・介護関係者等からのサポートが得られる体制も大切です。

重篤副作用疾患別対応マニュアルを日常業務で使ってみよう！

重篤副作用疾患別対応マニュアルは、
こちらのQRコードからご覧いただけます。

厚生労働省 ひと、くらし、みらいのために Ministry of Health, Labour and Welfare

一般社団法人　日本糖尿病学会

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5. Closing remark

Healthcare professionals are requested to continue to cooperate in the proper use of drugs by utilizing the Manuals and informing patients of them as necessary. The Manuals are available on the MHLW and PMDA websites.

[References]
MHLW website “Manuals for Management of Individual Serious ADRs”
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html
(only in Japanese)
PMDA website “Manuals for Management of Individual Serious ADRs” (intended for healthcare professionals)
https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html
(only in Japanese)

Previous articles introducing the Initiative of Revision of the Manuals for Management of Individual Serious ADRs (in English)
1. : Pharmaceuticals and Medical Devices Safety Information No.348
https://www.pmda.go.jp/files/000221054.pdf
2. : Pharmaceuticals and Medical Devices Safety Information No.357
https://www.pmda.go.jp/files/000226311.pdf
3. : Pharmaceuticals and Medical Devices Safety Information No.368
https://www.pmda.go.jp/files/000232763.pdf

Previous articles introducing the Manuals for Management of Individual Serious ADRs (in English)
1. : Pharmaceuticals and Medical Devices Safety Information No.393
https://www.pmda.go.jp/files/000247416.pdf
2. : Pharmaceuticals and Medical Devices Safety Information No.402
https://www.pmda.go.jp/files/000263297.pdf
3. : Pharmaceuticals and Medical Devices Safety Information No.407
https://www.pmda.go.jp/files/000266786.pdf

2

Revisions of PRECAUTIONS (No. 359)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated April 8, 2025.

1 Pituitary hormone preparations
Desmopressin acetate hydrate (injections)

Brand name	Desmopressin I.V. Injection 4 μg "Ferring" (Ferring Pharmaceuticals Co., Ltd.)
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Anaphylaxis

2 Antidiabetic agents
Imeglimin hydrochloride

Brand name	Twymeeg Tablets 500 mg (Sumitomo Pharma Co., Ltd.)
5. PRECAUTIONS CONCERNING INDICATIONS	(deleted)
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION **(newly added)**	Since the blood concentration of this drug increases due to delayed excretion of this drug in patients with renal impairment, attention should be paid to the following points: •In patients whose eGFR is greater than 10 mL/min/1.73 m^2 and less than 45 mL/min/1.73 m^2, the dose and dosing interval should be adjusted according to the table below.

eGFR (mL/min/1.73 m^2)	Dosing regimen
15 ≤ eGFR < 45	A dose of 500 mg, twice daily in the morning and evening
10 ≤ eGFR <15	A dose of 500 mg, once daily

•In particular, this drug should be administered to patients whose eGFR is greater than 10 mL/min/1.73 m^2 and less than 15 mL/min/1.73 m^2 only if the potential therapeutic benefits are considered to outweigh the potential risks. During administration of this drug, patients should be carefully monitored for their conditions. If further aggravation of renal function, etc. are observed, discontinuation of administration should be considered.
•Administration of this drug to patients whose eGFR is less than 10 mL/min/1.73 m^2 (including dialysis patients) is not recommended.

8. IMPORTANT PRECAUTIONS	Periodic renal function tests are recommended since the excretion of this drug is delayed and the blood concentration of this drug is

	increased. In particular, patients whose eGFR is less than 15 mL/min/1.73 m^2 should undergo frequent renal function testing and be closely monitored for the clinical course.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	Patients with renal impairment whose eGFR is less than 10 mL/min/1.73 m^2 (including dialysis patients) Administration of this drug is not recommended. The blood concentration of this drug may be increased markedly.
9.2 Patients with Renal Impairment (newly added)	Patients with renal impairment whose eGFR is greater than 10 mL/min/1.73 m^2 and less than 45 mL/min/1.73 m^2 The dose and the dosing interval should be adjusted according to the degree of renal impairment. In particular, this drug should be administered to patients whose eGFR is greater than 10 mL/min/1.73 m^2 and less than 15 mL/min/1.73 m^2 only if the potential therapeutic benefits are considered to outweigh the potential risks. Blood concentration of this drug will be increased.

3 Other antitumor agents

Enzalutamide

Brand name	Xtandi Tablets 40 mg, 80 mg (Astellas Pharma Inc.)
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	Patients receiving doravirine, ensitrelvir fumaric acid, lenacapavir sodium, or nirmatrelvir/ritonavir

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Doravirine Ensitrelvir fumaric acid Lenacapavir sodium Nirmatrelvir/ritonavir	The effects of these drugs may be attenuated by co-administration with enzalutamide.	The CYP3A4-inducing activity of enzalutamide may lead to a decrease in the blood concentration of these drugs.

4 Anti-virus agents

Nirmatrelvir/ritonavir

Brand name	Paxlovid Pack, Paxlovid Pack 300, 600 (Pfizer Japan Inc.)
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	Patients receiving the following drugs: Eletriptan hydrobromide, azelnidipine, olmesartan medoxomil/azelnidipine, eplerenone, amiodarone hydrochloride, bepridil hydrochloride hydrate, flecainide acetate, propafenone hydrochloride, quinidine sulfate hydrate, rivaroxaban, ticagrelor, anamorelin hydrochloride, rifabutin, blonanserin, lurasidone hydrochloride, pimozide, suvorexant, ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, ergometrine maleate, dihydroergotamine mesilate, methylergometrine maleate, finerenone, ivabradine hydrochloride, sildenafil citrate (Revatio), tadalafil (Adcirca), vardenafil hydrochloride hydrate, lomitapide mesilate, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], diazepam, clorazepate dipotassium, estazolam, flurazepam hydrochloride, triazolam, midazolam, voriconazole, apalutamide, carbamazepine, phenytoin, fosphenytoin

sodium hydrate, phenobarbital, mepenzolate bromide/phenobarbital, rifampicin, enzalutamide, food containing St. John's Wort

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Phenytoin Fosphenytoin sodium hydrate Phenobarbital Mepenzolate bromide/ phenobarbital Rifampicin Enzalutamide Food containing St. John's Wort	Antiviral activity may disappear, and resistance may occur.	The CYP3A4-inducing activity of these drugs may lead to a decrease in the blood concentration of nirmatrelvir and ritonavir.

3

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 March 31, 2025)
◎: Products for which EPPV was initiated after March 1, 2025

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
◎	Letermovir[*1] Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	March 27, 2025
◎	Marstacimab (genetical recombination) Hympavzi S.C. Injection 150 mg Pen	Pfizer Japan Inc.	March 24, 2025
◎	Teclistamab (genetical recombination) Tecvayli Subcutaneous Injection 153 mg, 30 mg	Janssen Pharmaceutical K.K.	March 19, 2025
◎	Mosunetuzumab (genetical recombination) Lunsumio for Intravenous Infusion 1 mg, 30 mg	Chugai Pharmaceutical Co., Ltd.	March19, 2025
◎	Datopotamab deruxtecan (genetical recombination) Datroway for Intravenous Drip Infusion 100 mg	Daiichi Sankyo Co., Ltd.	March 19, 2025
◎	Selexipag Uptravi Tablets for Pediatric 0.05 mg	Nippon Shinyaku Co., Ltd.	March 19, 2025
◎	Ozanimod hydrochloride Zeposia capsules 0.92 mg, Zeposia capsules starter pack	Bristol-Myers Squibb K.K.	March 19, 2025
◎	Tofersen Qalsody Intrathecal injection 100 mg	Biogen Japan Ltd	March 19, 2025
◎	Zanubrutinib Brukinsa capsules 80 mg	BeiGene Japan GK	March 19, 2025
◎	Patiromer sorbitex calcium Veltassa 8.4 g powder for suspension (single-dose package)	Zeria Pharmaceutical Co., Ltd.	March 17, 2025
◎	Flortaucipir (^{18}F) Tauvid Injection	PDRadiopharma Inc.	March 3, 2025

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Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
Insulin Icodec (genetical recombination) Awiqli injection FlexTouch 300 units, 700 units	Novo Nordisk Pharma Ltd.	January 30, 2025
Articaine hydrochloride/adrenaline bitartrate Septocaine Combination Injection Cartridge	GC SHOWAYAKUHIN CORPORATION	January 21, 2025
Amifampridine phosphate Firdapse Tablets 10 mg	DyDo Pharma, Inc.	January 15, 2025
Benralizumab (genetical recombination)*2 Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	December 27, 2024
Efgartigimod alfa (genetical recombination)/vorhyaluronidase alfa (genetical recombination)*3 Vyvdura Combination Subcutaneous Injection	argenx Japan K.K.	December 27, 2024
Daridorexant hydrochloride Quviviq Tablets 25 mg, 50 mg	Nxera Pharma Japan Co., Ltd.	December 19, 2024
Aceneuramic acid Acenobel Extended Release Tablets 500 mg	Nobelpharma Co., Ltd.	December 19, 2024
Estetrol hydrate/drospirenone alyssa combination tablets	Fuji Pharma Co., Ltd.	December 3, 2024
Donanemab (genetical recombination) kisunla Intravenous Infusion 350 mg	Eli Lilly Japan K.K.	November 26, 2024
Fruquintinib Fruzaqla capsules 1 mg, 5 mg	Takeda Pharmaceutical Company Limited	November 22, 2024
Sacituzumab govitecan (genetical recombination) Trodelvy for Injection 200 mg	Gilead Sciences K.K.	November 20, 2024
Amivantamab (genetical recombination) Rybrevant Intravenous Infusion 350 mg	Janssen Pharmaceutical K.K.	November 20, 2024
Repotrectinib Augtyro capsules 40 mg	Bristol-Myers Squibb K.K.	November 20, 2024
Mecobalamin*4 Rozebalamin for Injection 25 mg	Eisai Co., Ltd.	November 20, 2024
Teprotumumab (genetical recombination) Tepezza for Intravenous Infusion 500 mg	Amgen K.K.	November 20, 2024
Voclosporin	Otsuka Pharmaceutical	November 20,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
	Lupkynis Capsules 7.9 mg	Co., Ltd.	2024
	Tasurgratinib succinate Tasfygo Tablets 35 mg	Eisai Co., Ltd.	November 20, 2024
	Avibactam sodium/ceftazidime hydrate Zavicefta Combination for Intravenous Infusion	Pfizer Japan Inc.	November 12, 2024
	Tapinarof Vtama cream 1%	Japan Tobacco Inc.	October 29, 2024
	Gumarontinib hydrate Haiyitan tablets 50 mg	Haihe Biopharma K.K.	October 11, 2024
	Live attenuated influenza vaccine Flumist Intranasal Spray	Daiichi Sankyo Co., Ltd.	October 3, 2024

*1 Addition of a pediatric dosage for the indication below:
Prophylaxis of cytomegalovirus disease for the following:
•Allogeneic hematopoietic stem cell transplantation
•Organ transplantation

*2 Eosinophilic granulomatosis with polyangiitis in patients who have not sufficiently responded to conventional treatments

*3 Chronic inflammatory demyelinating polyradiculoneuritis

*4 Slowing the progression of functional impairment in amyotrophic lateral sclerosis (ALS)