Pharmaceuticals and Medical Devices Safety Information

No. 424 November 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

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Pharmaceuticals and Medical Devices Safety Information

No. 424 November 2025

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

[Outline of Information]

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.

6	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of September 30, 2025	31

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

ADR	Adverse Drug Reaction
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HPB	Health Policy Bureau
HRT	Hormone Replacement Therapy
MAH	Marketing Authorization Holder
MHLW	Ministry of Health Labour and Welfare
NDB	National Database of Health Insurance Claims and Specific Health Checkups of Japan
ODID	Office of Drug Induced Damage
OTC	Over-the-Counter
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division

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Summary of the Relief System for Adverse Drug Reactions and Request for Cooperation for the System

1. Introduction

The Relief System for Adverse Drug Reactions(ADRs)[1] (hereinafter referred to as “the Relief System”) was established in 1980 for the purpose of promptly relieving people suffering from adverse health effects such as diseases or disabilities that were caused by adverse reactions of pharmaceuticals, even if such pharmaceuticals were properly used. This is a public service funded by contributions etc. made by marketing authorization holders of pharmaceuticals to fulfill their social responsibilities.

A similar system for biological products, “the Relief System for Infections Derived from Biological Products” was established in 2004 to bring prompt relief to people who suffered from adverse health effects such as disorders or disabilities caused by viral infections, etc. acquired through using biological products despite proper use. Furthermore, adverse reactions to regenerative medical products and infections, etc. acquired through use of such products is now being covered by these relief systems since 2014.

However, adverse health effects resulting from vaccination (routine vaccination, temporary vaccination, etc.) in accordance with the Preventive Vaccination Law will not be covered by the Relief System but will be covered by the Relief System for Injury to Health with Vaccination based on the same law. In the case of voluntary vaccination,the Relief System or the Relief System for Infections Derived from Biological Products will be applicable.

Since April in 2024, the vaccination against the novel coronavirus has been positioned as a routine vaccination for category B diseases in accordance with the Preventive Vaccination Law for people who satisfy the following conditions: (1) the elderly aged 65 years or older, (2) people aged 60 years to 64 years who have disorders in the heart, kidney, or respiratory function that extremely restrict their activities of daily living, and those who have immune function disorders caused by human immunodeficiency virus that make it difficult for people to perform the activities of daily living. However, the opportunities to receive the relevant vaccination have also been secured as a voluntary vaccination for people other than the above. Therefore, please note that the relief system to be claimed will differ depending on the conditions such as date of vaccination and whether or not the vaccination is a routine vaccination. For details, refer to “Handling of relief measures for adverse health effects caused by vaccination against novel coronavirus after FY 2024” (Administrative Notice issued jointly by the Division of Vaccination, Department of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labour and Welfare/the Office of Drug-Induced Damages at the General Affairs Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated March 11, 2024)[2].

In the Relief System, a decision of benefit payment has been made for 31,515 cases since the establishment of the system in 1980 to the end of 2024. People suffering from adverse health effects due to adverse drug reactions are often informed of the Relief System by physicians, pharmacists, and other healthcare professionals. Healthcare professionals are asked to cooperate

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[1] The Relief System (PMDA website): https://www.pmda.go.jp/relief-services/outline/0001.html
Documents required for claiming a relief benefit:https://www.pmda.go.jp/relief-services/adr-sufferers/0004.html

[2] Administrative Notice: https://www.mhlw.go.jp/content/001223621.pdf

for provision of information on the Relief System and preparation of medical certificates, etc. necessary for claiming a relief benefit (see page 13).

2. Adverse Health Effects Subject to benefits for the Relief System

Adverse health effects Subject to benefits for the Relief System are diseases (those which require hospitalization), disabilities (those which significantly restrict daily activities), or death that occur despite proper use of drugs or regenerative medical products (hereinafter referred to as “drugs, etc.”).

Drugs, etc. subject to the Relief System include those which are prescribed or used at hospitals/clinics or those which are purchased at pharmacies, etc. However, some drugs, etc. such as anticancer drugs and immunosuppressants are excluded from the Relief System. Furthermore, for claiming a relief benefit for the diseases, the deadline for claiming is within 5 years since the payment of costs has been specified.

[Types and amounts of relief benefits (as of April 1, 2025)]
Medical Expenses (costs borne by the patients, not including health insurance payments)
- Actual costs of treatment for disease caused by ADRs etc. will be compensated.

Medical Allowance (37,900 or 39,900 yen per month)
- Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs

Disability Pension (Grade 1: 3,045,600 yen per year; Grade 2: 2,436,000 yen per year)
- Benefits are provided to compensate for living costs, etc., of patients aged 18 or older, who suffer from a certain degree of disabilities caused by ADRs, etc.

Pension for Raising Children with Disabilities (Grade 1: 952,800 yen per year; Grade 2: 762,000 yen per year)
- Benefits are provided for people who are responsible for raising children under 18 who suffer from a certain degree of disabilities caused by ADRs, etc.

Bereaved Family Pension (2,664,000 yen per year)
- Benefits are provided for bereaved families to rebuild their lives following the deaths of their main providers from ADRs, etc.

Lump-Sum Benefits for Bereaved Family (7,992,000 yen)
- Benefits are provided for bereaved families for condolence and sympathy following the death from ADRs, etc. of their family member who is not the main provider.

Funeral Expenses (219,000 yen)
- Benefits are provided for the costs of holding funerals for people who died from ADRs, etc.

3. Degree of Awareness of the Relief System

According to the survey conducted in 2024, awareness of the Relief System among the general public was 26.3% in total: 6.3% of the subjects answered that they “are aware of” the Relief System and 20.0% answered that they “have heard about” the Relief System. It is inferred that some people may not file an application for compensation for adverse health effects associated with ADRs they have suffered because they are unaware of the Relief System.

On the other hand, awareness among healthcare professionals was 82.4% in total: 57.5% of the subjects answered that they “are aware of” the Relief System and 24.9% answered that they “have heard about” the Relief System. By occupational category, the awareness was 92.6% of physicians, 97.2% of pharmacists, 56.9% of nurses, and 84.2% of dentists, and 74.5% of medical social workers. Among the healthcare professionals who are aware of the system, the proportion of those who were involved in a filing procedure was 9.5% in total: 13.4% of physicians, 10.2% of pharmacists, 4.2% of nurses, 4.2% of dentists, and 20.3% of medical social workers. Note 1)

Since April 2016, a section on “Channels of acquisition of information on the Relief Systems” (Choice from among “Physician,” “Dentist,” Pharmacist,” “Other medical institution staff,” “Newspaper/TV, etc.,” and “Other”) was added to all claim forms related to relief benefits to grasp the channels of acquisition of information on the relief system. The most common channels in the

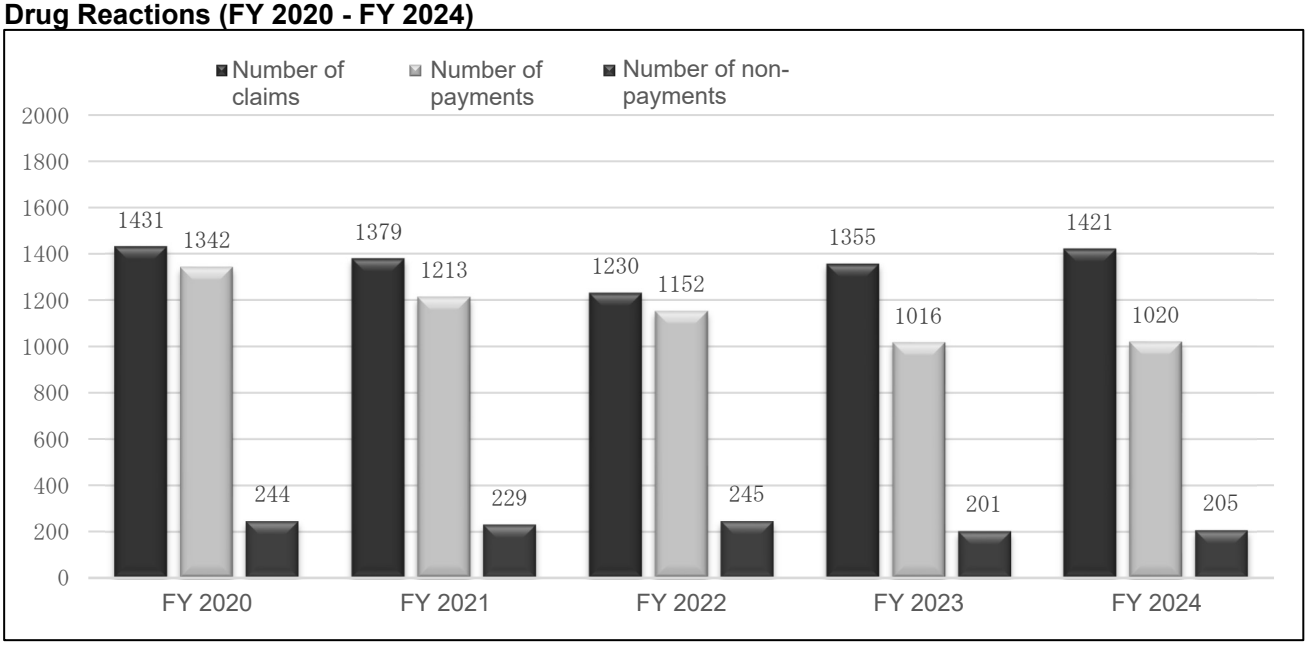
claim form submitted in FY 2024 were physicians in 450 cases (30.1%), followed by Other (internet) in 275 cases (18.4%), and pharmacists in 144 cases (9.6%) (multiple choices allowed) [Note 1)]

4. Status of Payment/Non-payment in the Relief System

Figure 1 shows the annual changes in the number of claims and payments in the Relief System from FY 2020 to FY 2024. In FY 2024, the number of claims was 1,421, and payments were made for 1,020 claims and non-payments were decided for 205 claims. Figure 2 shows the proportions of payments and non-payments and the breakdown of reasons for non-payments between FY 2020 and FY 2024.

In addition, the standard administrative processing time [Note 2)] from when Pharmaceuticals and Medical Devices Agency (PMDA) receives an application to when PMDA notifies the applicant of the decision was within 6 months, and achievement of this standard administrative processing time in 65% (60% until FY 2022) or more of cases for which payment or non-payment was determined has been set as a goal. The actual achievement percentage in FY 2024 was 88.2%, which was significantly higher than 65%.

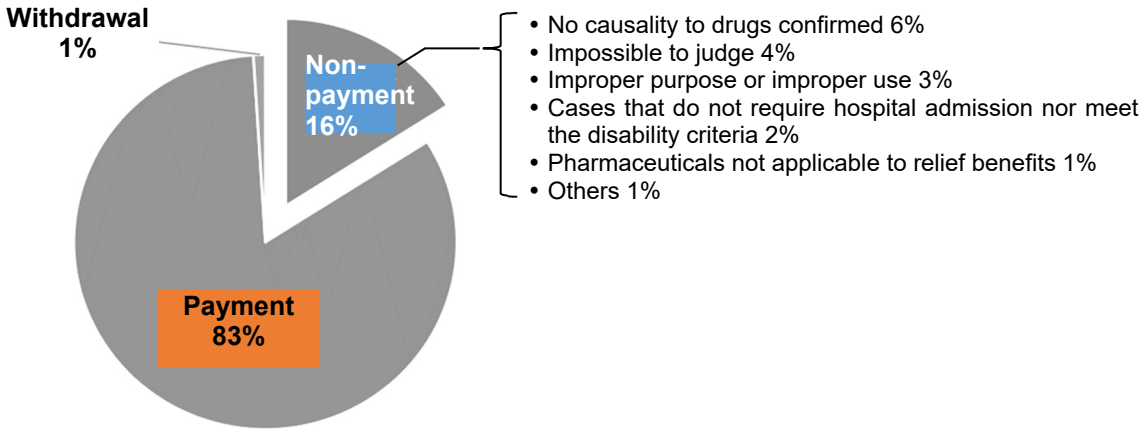
Figure 1 Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY 2020 - FY 2024)



(Explanation about the graph)

* The number of cases represents the number of claimants, and a second claim for the same cause was counted as a single case.
* The number of applications and the total number of payment and non-payment are not necessarily consistent since several months are required from the receipt of the application to the decision of benefit payment.

Figure 2 The proportions of payments and non-payments and the breakdown of reasons for non-payments (FY 2020 - FY 2024)



5. Cases Approved/Not Approved for Relief Benefits

5-1. Cases approved for relief benefits

<Case 1> Case provided Medical Expenses and Medical Allowance for aseptic meningitis caused by mumps vaccine

A female in her 10s. The patient had aseptic meningitis after receiving a mumps vaccine and was admitted to the hospital for treatment, for which medical expenses and medical allowance were paid.

<Case 2> Case provided Medical Expenses/Medical Allowance/Bereaved Family Pension/Funeral Expenses for anaphylactic shock caused by iopromide, resulting in death.

A man in his 50s. The patient had anaphylactic shock after using iopromide, which resulted in death, for whom medical expenses/medical allowance/bereaved family pension/funeral expenses were paid.

<Case 3> Case provided Medical Expenses, Medical Allowance, and Disability Pension for cerebral hemorrhage caused by clopidogrel and aspirin and consequent limb function disorder, mastication/swallowing function disorder, and speech function disorder

A female in her 50s. The patient had cerebral hemorrhage after using clopidogrel and aspirin and was admitted to the hospital for treatment, and then experienced limb function disorder, mastication/swallowing function disorder, and speech function disorder associated with cerebral hemorrhage, for whom medical expenses, medical allowance, and disability pension were paid.

<Case 4> Case provided Medical Expenses and Medical Allowance for oculomucocutaneous syndrome caused by an OTC drug

A female in her 20s. The patient had oculomucocutaneous syndrome after using Eve® A Tablets and was admitted to the hospital for treatment, for whom medical expenses and medical allowance were paid.

5-2. Cases not approved for relief benefits (cases in which method of use of pharmaceutical was not considered proper)

Of the 1,124 cases of non-payment between FY 2020 and FY 2024 [Note 3)], the reason for non-payment was improper purpose or improper use in 3% (Figure 2). Table 1 shows the most common pharmaceuticals for which method of use was not considered proper.

Of the cases not approved for relief benefits, the specific cases for which the method of use was not considered proper in the past 1 year or so are presented.

Table 1 The number of cases for which method of use of pharmaceutical was not considered proper (FY 2020 - FY 2024)

Name of causative drug	FY 2020	FY 2021	FY 2022	FY 2023	FY 2024	Total (cases)
Lamotrigine	8	5	3	12	4	32
Human chorionic gonadotrophin	2	4	5	5	3	19
Lithium carbonate	0	3	4	0	4	11
Methotrexate	5	1	0	2	3	11
Thiamazole	4	2	0	3	1	10
Others	16	22	21	18	22	99
Total (cases)	35	37	33	40	37	182

(1) Cases where pharmaceuticals were used in ways other than the approved dosage and administration

Cases using lamotrigine still tend to account for a large majority of cases for which pharmaceuticals were used in ways other than the approved dosage and administration.

Healthcare professionals should confirm the electronic package insert once again and pay attention to the dosage and administration when using pharmaceuticals.

<Case 1> Case of disseminated erythematous papular drug eruption caused by lamotrigine (when titrating)

A female in her 20s. Lamotrigine was used for epilepsy based on the prescription that did not contain concomitant sodium valproate and contained a drug other than drugs that induce glucuronidation of lamotrigine as a concomitant drug. The administration was started at a dose of 25 mg/day. However, the dose was increased to 50 mg/day 5 days after the administration start, and therefore, the method of use was not considered proper.

<Case 2> Case of erythema multiforme-type drug eruption caused by lamotrigine (when initiating administration)

A female in her 30s. Lamotrigine was used for bipolar disorder and started at a dose of 50 mg/day as a monotherapy, and therefore, the method of use was not considered proper.

Improper use of lamotrigine

It has been demonstrated in Japanese clinical trials that the incidence of skin disorders increases when lamotrigine is administered at doses or frequencies higher than recommended, and precaution has been provided to comply with the dosage and administration since the approval of Lamictal Tablets® in October 2008. However, serious skin disorders have been continuously reported even after that, and therefore, healthcare professionals have been repeatedly encouraged to adhere to the recommended administration and dosage, including dosage when initiating administration and dosage when titrating, as well as alternate-day administration and when to titrate, through various means including the distribution of request for proper use [Note 4)] in January 2012 and the Dear Healthcare Professional Letter of Rapid Safety Communication (Blue Letter) in February 2015 from PMDA.

In spite of such precautions, cases in which a claim made for occurrence of adverse reactions ends up as non-payment because proper use was not confirmed have still continuously occurred. Thus, in October 2019, PMDA distributed requests for proper use of drugs [Note 5)] to repeatedly provide precautions.

Many of the cases where payment was not approved due to improper use included prescription of excessive dosages during initial administration or during titration up to a maintenance dose, or non-adherence to dose increase intervals.

Dosage and administration of lamotrigine are closely regulated in terms of dosages and dose increase intervals depending on specific indications and concomitant pharmaceuticals. Examples of the dosage and administration of the original drug (Lamictal Tablets®) in adults when used "for suppression of recurrent/relapsed mood episodes in patients with bipolar disorder" described in the electronic package insert are presented below. In addition to these examples, other dosage and administration should be confirmed with the latest electronic package insert when using this drug.

Descriptions of the electronic package insert of Lamictal Tablets® (lamotrigine) (revised in May 2025) (excerpt)

When used for suppression of recurrent/relapsed mood episodes in patients with bipolar disorder (adults)

	Combination therapy			
Types of drugs concomitantly used with this drug	(2) Co-administration with sodium valproate	(3) Without co-administration with sodium valproate Note 1)		(1) Monotherapy
		(3)-i) Co-administration with drugs that induce glucuronidation of this drug Note 2)	(3)-ii) Co-administration with drugs other than (3)-i) Note 3)	
Weeks 1 and 2	25 mg every other day	50 mg/day (Once daily)	25 mg/day (Once daily)	
Weeks 3 and 4	25 mg/day (Once daily)	100 mg/day (Administered in 2 divided doses per day)	50 mg/day (Administered once daily or in 2 divided doses per day)	
Week 5	50 mg/day (Administered once daily or in 2 divided doses per day)	200 mg/day (Administered in 2 divided doses per day)	100 mg/day (Administered once daily or in 2 divided doses per day)	
At and after Week 6	100 mg/day (Up to 200 mg/day) (Administered once daily or in 2 divided doses per day) (The dose may be increased by up to 50 mg/day at intervals of at least 1 week.)	300 mg/day at Week 6 300 to 400 mg/day at and after Week 7 (Up to 400 mg/day) (Administered in 2 divided doses per day) (The dose may be increased by up to 100 mg/day at intervals of at least 1 week.)	200 mg/day (Up to 400 mg/day) (Administered once daily or in 2 divided doses per day) (The dose may be increased by up to 100 mg/day at intervals of at least 1 week.)	

This drug is primarily metabolized by glucuronosyltransferase.

*1) In combination therapy with drugs that may not affect glucuronidation of this drug, the dosage and administration when co-administered with sodium valproate should be followed.

*2) Drugs that induce glucuronidation of this drug: phenytoin, carbamazepine, phenobarbital, primidone, rifampicin, lopinavir/ritonavir combination drug

*3) Drugs that do not affect glucuronidation of this drug:

Aripiprazole, olanzapine, zonisamide, gabapentin, cimetidine, topiramate, pregabalin, lithium, levetiracetam, perampanel, lacosamide

(2) Case where required tests are not performed

If electronic package inserts specify that certain tests must be conducted for use of pharmaceuticals and these tests are not conducted, the method of use may not be considered proper.

In order to detect ADRs early and prevent them from becoming serious, healthcare professionals are encouraged to confirm the descriptions of the electronic package inserts again as implementation of appropriate tests and explanations to patients regarding the need for such tests so that they can understand it are considered important.

<Case 1> Case of lithium poisoning with use of lithium carbonate

A man in his 50s. Lithium serum concentration had not been measured at all while the patient was taking lithium carbonate at a maintenance dose for approximately seven years until lithium poisoning was detected, and therefore the method of use was not considered proper.

Description of electronic package insert of lithium carbonate 100 mg "AMEL" (revised in November 2024) (excerpt)

[PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION]
Lithium poisoning may occur as a result of an overdose. The serum lithium level should be measured about once weekly at the initial phase of administration and during the dose-increase phase until the maintenance dose is fixed, and about once every 2 to 3 months during the maintenance dose phase. Lithium carbonate should be used while assessing a trough level based on the results of lithium level measurement. If the patient has any factor that may increase the serum lithium level (e.g., lack of food and water intake, susceptibility to dehydration, concomitant use of drugs that may increase the serum lithium level such as nonsteroidal anti-inflammatory drugs), or any initial symptom of lithium poisoning, serum lithium level should be measured.

Tests not conducted when using lithium carbonate

Lithium carbonate may cause poisoning when overdosed, and therefore it is required that lithium carbonate be used while periodically measuring the lithium serum concentration and assessing the trough level. Also, lithium carbonate is contraindicated in patients prone to develop lithium retention such as patients with renal impairment. Alerts have been issued in many ways using notifications on proper use, etc. from PMDA and various materials, but cases of non-conduct of tests have still been found. In September 2025, the PMDA again issued a Request for Proper Use of Drugs "Compliance with Measurement of Blood Concentration during Treatment with Lithium Carbonate". Healthcare professionals are encouraged to confirm the implementation of blood concentration measurement during the treatment period.

<Case 2> Case of agranulocytosis associated with thiamazole

A female in her 50s. During treatment with thiamazole, blood tests including differential leukocyte count had not been conducted for 30 days until detection of agranulocytosis, and therefore, the method of use was not considered proper.

Descriptions of the electronic package insert of MERCAZOLE Tablet® (thiamazole) **(revised in June 2025)** (excerpt)

[WARNING]
Serious agranulocytosis has been reported especially within the first 2 months after administration, leading to fatal outcomes in some cases. Blood tests including differential leukocyte count should be performed once every 2 weeks in principle for at least 2 months after administration, and periodically after that. If any abnormalities such as decreasing tendency of granulocytes are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. The same caution should be exercised when administration is resumed after the temporary discontinuation.

(3) Cases where patients take the drugs by self-judgment instead of following physicians' instructions

Cases where a prescription drug prescribed by a physician was used based on the patient's self-judgment not based on the instruction of the physician or a prescription drug prescribed to someone other than the patient, such as a family member or acquaintance, was used are not considered to be the cases where drugs are used for the proper purpose and with the proper method.

Healthcare professionals are encouraged to give certain guidance such as specific instructions on the date of administration, dosing conditions, and dose so that patients can take drugs properly.

<Case> Case of erythema multiforme-type drug eruption caused by garenoxacin

A female in her 50s. Use of garenoxacin for residual urine and pollakiuria resulted in the occurrence of erythema multiforme-type drug eruption. The patient took the unused drugs that were previously prescribed based on her self-judgment without instructions from the physician, and therefore, the method of use was not considered proper.

(4) Cases of use in patients corresponding to "CONTRAINDICATIONS"

Cases where the drug was used in patients even though the patients correspond to "CONTRAINDICATIONS" and the method of use was not considered proper.

Healthcare professionals are encouraged to use drugs properly after fully considering the condition of patients using the drugs and contraindications of the drugs.

<Case> Case where cefdinir tablet was used in a patient with a history of allergy

A female in her 30s. Cefdinir tablet was prescribed for the patient even though the patient had a history of allergy to cefdinir, which resulted in occurrence of anaphylaxis. Therefore, the method of use was not considered proper.

Description of electronic package insert of CEFDINIR Tablets 100 mg "SAWAI" (revised in November 2023) (excerpt)

2. CONTRAINDICATIONS (This drug is contraindicated in the following patients.) Patients with a history of hypersensitivity to any of the ingredients of this drug

Healthcare professionals are encouraged to confirm the descriptions of the electronic package insert again to make efforts for proper use.

Notification on proper use, etc. of drugs
https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/properly-use-alert/0003.html

6. Source of Information on the Relief System

The Ministry of Health, Labour and Welfare issued a request for cooperation in the preparation of documents required for claiming relief benefits (repeated information provision) in July and a notification for cooperation in the preparation of documents under the Relief System for Adverse Drug Reactions (information provision) in August 2025. See the descriptions of the notification (excerpts) presented below.

1. Preparation of documents required for claiming a relief benefit concerning the relief system
   In claiming a relief benefit under the relief system, people who suffered from adverse health effects need to make a claim to the PMDA by submitting the claim form together with necessary documents such as medical certificate and certificate of medical examination, or proof of purchase if the drug was bought from pharmacies, etc.
   Your associations are encouraged to inform the members of your associations that they will be requested to cooperate for preparation of documents required for claiming a relief benefit concerning the relief system while fully understanding the purpose of the system and documents (*) in the case where a person who desires to make a claim asks them for preparation of medical certificate, etc. at a medical institution or a pharmacy so that the claim will be smoothly processed. Please note that healthcare professionals are required to respond to a request for a medical certificate appropriately because it is not allowed to refuse the request without legitimate grounds pursuant to the provisions of Article 19, Paragraph 2 of the Medical Practitioners' Act (Act No. 201 of 1948).
   *Since it is not necessary to prove the causal relationship between the drug and the adverse health effects in the medical certificate required for claiming a relief benefit, the actual symptoms of the claimant and details of the treatment should be described as they were. Matters concerning medical and pharmaceutical judgments, such as causal relationship and whether the proper use was confirmed or not, will be determined on a case-by-case basis by the Pharmaceutical Affairs Council established at the Ministry of Health, Labour and Welfare. Even if the claim ends up as non-payment because the drug was not used properly, PMDA will not pursue the responsibility of healthcare professionals.

From the Notification, the Administrative Notice dated July 7, 2025 issued jointly by the Director of the Office of Drug-Induced Damages at the General Affairs Division, the Director of Safety Division, Pharmaceutical Safety Bureau, and the Director of Professions Division, Health Policy Bureau "Request for Cooperation for the Preparation of Documents, etc. in the 'Relief System for Adverse Drug Reaction' (Repeated notification)" (PSB/ODID Notification No. 0707-3, PSB/SD notification No. 0707-5, HPB/PD Notification No. 0707-7)

1. Support for preparation of documents required for claiming a relief benefit concerning the relief system
   In claiming a relief benefit under the relief system, people who suffered from adverse health effects need to make a claim to the PMDA by submitting the claim form together with necessary documents such as medical certificate and certificate of medical examination, or proof of purchase if the drug was bought from pharmacies, etc. (hereinafter referred to as "documents for claim")
   Your associations are encouraged to inform the members of your associations that they will be requested to cooperate for preparation of documents required for claiming a relief benefit concerning the relief system while collaborating with professionals who prepare the medical certificate, etc. based on full understanding of the purpose of the system and documents (*) in the case where a person who desires to make a claim asks them for preparation of medical certificate, etc. at a medical institution or a pharmacy so that the person suffering the adverse health effects can smoothly make a claim.
   *It is not necessary to prove the causal relationship between the drug and the adverse health effects in the medical certificate required for claiming a relief benefit. The professionals need to

be informed that the actual symptoms of the claimant and details of the treatment should be described as they were. Matters concerning medical and pharmaceutical judgments, such as causal relationship and whether the proper use was confirmed or not, will be determined on a case-by-case basis by the Pharmaceutical Affairs Council established at the Ministry of Health, Labour and Welfare. Even if the claim ends up as non-payment because the drug was not used properly, PMDA will not pursue the responsibility of healthcare professionals.

From the Notification, the Administrative Notice dated August 25, 2025 issued jointly by the Director of the Office of Drug-Induced Damages at the General Affairs Division and the Director of Safety Division, Pharmaceutical Safety Bureau "Request for Cooperation for the Preparation of Documents, etc. in the 'the Relief System for Adverse Drug Reactions' (Information provision)" (PSB/ODID Notification No. 0825-01, PSB/SD Notification No. 0825-01)

For details of the Relief System and Relief System for Infections Derived from Biological Products, refer to the PMDA website (https://www.pmda.go.jp/relief-services/index.html). Furthermore, materials on the Relief System for patients are also available on the website, and healthcare professionals are encouraged to use these materials to disseminate information on the Relief System.

Necessary documents for making claims can be downloaded from the following website and can be created using a computer, etc.

Furthermore, if the documents are created using a computer, etc., claimants are requested to submit the paper-based documents as well as provide an electronic copy of the electronic file using a compact disk, etc.

the Relief System
https://www.pmda.go.jp/relief-services/adr-sufferers/0004.html
Relief System for Infections Derived from Biological Products
https://www.pmda.go.jp/relief-services/infections/0007.html

Details of medical certificates and certificates for prescription/use are important information when judging whether or not use was proper, etc.; therefore, as many details as possible should be included in these documents. Healthcare professionals are also encouraged to use the preparation guidelines for medical certificates.

Please note that the following cases will not be applicable to receive relief benefits.

a. Cases of adverse health effects resulting from vaccination practice in accordance with Preventive Vaccination Law (Relief System for Injury to Health with Vaccination is applicable in accordance with the Preventive Vaccination Law.) However, cases of adverse health effects resulting from voluntary vaccinations are eligible for relief benefits.
b. Cases where it is clear who is responsible for adverse health effects, including in the case of product liability of the marketing authorization holders of the pharmaceutical or biological product. Note 6)
c. Cases where it is necessary to use the pharmaceutical or biological product in an amount exceeding the approved dosage for the purpose of saving the patient's life, even if it was recognized beforehand that adverse health effects may occur. Note 7)
d. Cases where it is not confirmed that the drug or biological product is used for a proper purpose and with a proper method.
   (e.g., cases where the drug or biological product has been used in ways other than indications approved by the Minister of Health, Labour and Welfare, or cases where the drug or biological product have not been used in accordance with the Precautions section in the electronic package inserts)
e. Cases of adverse health effects caused by drugs inapplicable for the relief benefits
   Drugs inapplicable for the relief benefits Note 8) include:

(1) Pharmaceuticals used for the purpose of the treatment of cancer or other specific diseases designated by the Minister of Health, Labour and Welfare (anticancer drugs and immunosuppressant, etc.).
(2) Drugs that do not have the possibility to cause adverse reactions, including drugs not used directly on human bodies or drugs without pharmacological effects (insecticides, disinfectant agents, and in vitro diagnostics, etc.)

f. Cases of mild adverse health effects (including a case where admission to a hospital or treatment equivalent to inpatient care is not required) or cases where disabilities caused by pharmaceuticals fail to meet the disability criteria under the relief system [Note 9)].
g. Cases where the deadline for claiming the relief benefits has passed.
h. Other cases that have not been approved by the Pharmaceutical Affairs Council, MHLW based on medical and pharmaceutical judgment.
   - Cases where the disorders or disabilities are considered to be unlikely to be caused by ADRs (those that are not considered to be due to drugs)
   - Cases where it cannot be judged whether there are causalities or whether pharmaceuticals are used for the proper use and with the proper method, because of insufficient documentation (impossible to judge)

7. Conclusion

Healthcare professionals are encouraged to fully check necessary alerts in the electronic package inserts before using drugs and to use them properly. Please note that cases where drugs are not used properly may not be applicable to receive relief benefits under the Relief System even if the adverse health effects are suspected to be ADRs related to drugs. Regarding the indication for use of drugs, etc., drugs used as off-label use are inapplicable for the relief benefits unless they are widely used in medical practice based on a certain level of evidence, such as cases where the use of these drugs are described in the guidelines.

Also, since June 2014, a section for questions about the Relief System has been added to the “Drug Safety Information Report” form, which is an adverse reaction report form from healthcare professionals, and answer options to the questions such as “Patient plans to make a claim” and “Already introduced to the patient” are provided. Healthcare professionals are encouraged to introduce the Relief System to patients when reporting adverse reactions.

If ADRs, etc. occur or if healthcare professionals are consulted by their patients about ADRs, healthcare professionals should provide information on the Relief System to the patient or family members if the adverse health effects are possibly applicable to receiving relief benefits under the Relief System. MHLW/PMDA encourages continued cooperation from healthcare professionals in preparing documents, such as medical certificates, required to claim these relief benefits.

For the details of the Relief System, see the website below. The e-learning course also introduces the flow of claiming and case examples of payments and non-payments.

https://www.pmda.go.jp/kenkouhigai_camp/

The following consultation service in regard to the Relief System is available (same service provided for Relief System for Infections Derived from Biological Products).

- Relief System Consultation Service, PMDA
  Phone: 0120-149-931 (toll-free)
  Office hours: Monday to Friday 9:00-17:00 (excluding national and New Year holidays)
  E-mail: kyufu@pmda.go.jp

Note 1) Based on “FY 2024 Awareness Survey on the Relief System for Adverse Drug Reaction” and https://www.pmda.go.jp/relief-services/adr-sufferers/0023.html
“FY 2025 Committee on Relief Services” (Pharmaceuticals and Medical Devices Agency).
https://www.pmda.go.jp/about-pmda/advisory-council-information/relief-services/0060.html

Note 2) The periods during which administrative processing cannot be conducted, because of the need for additional or supplemental documents from claimants and medical institutions for the purposes of making medical and pharmaceutical judgments, are excluded from the administrative processing time from claim submission to payment approval/rejection judgments.

Note 3) The number of cases represents the number of claimants, and a second claim for the same cause was counted as a single case.

Note 4) Compliance with Dosage and Administration and Ensuring Early Detection for Lamictal Tablets (lamotrigine)-induced Serious Skin Disorders
https://www.pmda.go.jp/files/000145676.pdf

Note 5) Compliance with Dosage and Administration and Ensuring Early Detection for lamotrigine-induced Serious Skin Disorders
https://www.pmda.go.jp/files/000231981.pdf

Note 6) “Person responsible for payment of damages” typically refers to person in charge, etc. for accidents due to adulterated drugs such as mutated drugs or contaminated drugs.

Note 7) If the sufferer’s acceptance towards the ADR that occurred is a socially accepted concept. Typical situations in which such acceptance is anticipated are as follows:
(1) The pharmaceutical is used for critical care situations.
(2) There are no alternative treatment modalities available.
(3) A higher dose of the pharmaceutical than the recommended dose is used.
(4) The possibility of adverse health effects due to ADRs was recognized in advance.
(5) Adverse health effects due to ADRs which were recognized in advance as mentioned in (4) occurred.

Whether individual cases will be accepted will be judged based on these typical situations. In order for the claim to be considered acceptable, similar acceptance in terms of social acceptance must be necessary. In such cases, even if the aforementioned 5 criteria are not all satisfied, cases will be judged based on whether they are in accordance with a typical case from an overall standpoint including other situations or factors, etc.

Note 8) Drugs, etc. inapplicable for the relief benefits
https://www.pmda.go.jp/relief-services/adr-sufferers/0044.html

Note 9) Degree of disability does not meet the criteria of “Disability that prevents a person from performing daily life activities by himself/herself (Grade 1)” or “Disability that results in significant limitations during his/her daily life performance (Grade 2)”

1－2

Relief Efforts for Human Papilloma Virus Vaccine Through the Relief System for Adverse Drug Reactions

1. Introduction

Based on the joint meeting of the Adverse Reaction Review Committee for Preventative/Voluntary Vaccination on the Health Sciences Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council in regard to the human papillomavirus vaccine (hereinafter referred to as “HPV vaccines”) held on September 17, 2015, under the Relief System, MHLW/PMDA have promptly reviewed the relief claims for claimants who claim adverse health effects for symptoms that occurred after administration of HPV vaccines and have taken efforts to increase awareness of the Relief System. As a result, the number of people for whom it was confirmed that the causal relationship with the HPV vaccination cannot be ruled out by the end of March 2025 was 321 out of a total of 540 people reviewed.

People who received vaccination based on “Urgent Vaccination Promotion such as for cervical cancer vaccines” conducted between November 26, 2010 and March 31, 2013 Note) may be eligible to receive support for medical expense/medical allowance payments from Public Foundation of the Vaccination Research Center where the causal relationship between the adverse health effects and the HPV vaccine cannot be ruled out based on the review results of the relief benefits; for example, even if the medical care required was not sufficient to be considered inpatient care, such as when patients received treatment on an outpatient basis.

If support for medical expenses/medical allowances is to be provided for the first time for any adverse health effect that occurred after vaccination in this program, claims for relief benefits must first be submitted for the Relief System regardless of the degree of the treatment; that is, outpatient or inpatient; therefore, healthcare professionals are requested to cooperate with claimant’s procedures (creating medical certificates, etc.).

MHLW will continue to offer necessary support for patients while promptly reviewing the relief claims.

Note) Females who are first year junior high students (approximately 13 years old) to those who are first year high school students (approximately 16 years old) in whom HPV vaccines were administered in the period from November 26, 2010 to March 31, 2013 are possibly eligible to receive relief benefits.
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/sesshu_youryou.pdf

2. Performance of the Relief Service for Adverse Health Effects under the Relief System

The performance of the relief service for adverse health effects associated with HPV vaccines under the Relief System (changes by fiscal year) are reported as shown in the table below. Note)

Fiscal year	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015
Number of claims	2 cases	10 cases	7 cases	25 cases	39 cases	152 cases
Number of cases for which payment was determined	0 cases	5 cases	9 cases	8 cases	4 cases	75 cases
Fiscal year	FY 2016	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021
Number of claims	334 cases	141 cases	86 cases	59 cases	34 cases	20 cases
Number of cases for which payment was determined	314 cases	223 cases	111 cases	75 cases	49 cases	29 cases
Fiscal year	FY 2022	FY 2023	FY 2024	Total		
Number of claims	9 cases	6 cases	10 cases	(934)		
Number of cases for which payment was determined	8 cases	13 cases	3 cases	(926)		

(From PMDA: "OPERATING PERFORMANCE FOR FY 2024" cited from https://www.pmda.go.jp/about-pmda/annual-reports/0001.html)

Note) More than one type of benefits may be claimed in one case of claim. Furthermore, one claimant may make a claim continuously.

3. Items to Be Considered in Regard to Necessary Documentation When Claiming Relief Benefits under the Relief System in Relation to HPV Vaccines, etc.

In 2016, MHLW issued an administrative notice regarding items to be considered in regard to necessary documentation when claiming relief benefits. See the descriptions of the notification presented below.

1. About medical certificates
   (1) Medical certificates are only required for medical care related to the adverse health effect the claims are being filed for, regardless of whether the care is provided on an inpatient or outpatient basis. Claimants do not need to request for medical certificates to be created by all medical institutions they visited.
   (2) For the medical certificates, information necessary to judge the causal relationship with the vaccination, such as information regarding day of vaccination and the clinical course until onset of symptoms, is considered important and healthcare professionals are encouraged to cooperate in providing information as much as possible. Furthermore, it is permissible for the medical institution creating the medical certificate to include information other than treatment (for example, information related to the duration of clinical practice where the patient consulted multiple medical institutions since the symptoms were not apparent, symptoms that triggered hospital consultation, etc.).
   Please also cooperate in attaching materials related to other medical institutions (addresses, telephone numbers, day of consultation, medical chart number, name of physician in charge, symptoms that triggered hospital consultation, etc.) even if the material is created by the claimant and not the medical institution or materials that only have partial information.
2. About certificates for prescription/use
   (1) If the vaccine was administered by the physician or medical institution that created the

medical certificate, certificates for prescription are unnecessary.

(2) If possible, please request vaccination coupons provided prior to vaccination or other reference materials (such as body temperature results, items asked during medical interview or examined) and attach these to the claims.

From the administrative notice issued on January 14, 2016 by the Safety Division of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare "Items to be considered in regard to necessary documentation when claiming relief benefits under the Relief System for Adverse Drug Reactions in relation to administration based on 'Urgent Vaccination Promotion such as for cervical cancer vaccines'."

[References]

• Notification by the Director of the Health Service Bureau, Ministry of Health, Labour and Welfare and by the Director of the Sports and Youth Bureau, Ministry of Education, Culture, Sports, Science and Technology, dated September 30, 2015, "Enhancing consultation/support services for those who developed symptoms after vaccination for HPV infections" (Health Safety Bureau, MHLW Notification No. 0930-7, 27Sports and Youth Bureau, Ministry of Education, Culture, Sports, Science and Technology Notification No. 419)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/madoguchi/dl/151116_02.pdf (only in Japanese)

• Administrative notice issued on October 22, 2015 by Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare/Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare "(Request for) Increasing awareness of deadlines for the Relief System for Adverse Drug Reactions claims in relation to administration based on 'Urgent Vaccination Promotion such as for cervical cancer vaccines' "
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/dl/yobou151022-1.pdf (only in Japanese)

• Administrative notice issued on December 1, 2015 by Health Service Division, Health Service Bureau, Ministry of Health, Labour and Welfare "(Request for) Relief benefits for adverse health effects due to Urgent Vaccination Promotion such as for cervical cancer vaccines"
https://www.pmda.go.jp/files/000208632.pdf (only in Japanese)

• Administrative notice issued on January 14, 2016 by the Safety Division of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare "Items to be considered in regard to necessary documentation when claiming relief benefits under the Relief System for Adverse Drug Reactions in relation to administration based on 'Urgent Vaccination Promotion such as for cervical cancer vaccines'."
https://www.pmda.go.jp/files/000209731.pdf (only in Japanese)

• Notification dated July 7, 2025 issued jointly by the Director of the Office of Drug-Induced Damages at the General Affairs Division, the Director of Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, and the Director of Professions Division, Health Policy Bureau "Request for Cooperation for the Preparation of Documents, etc. in the Relief System for Adverse Drug Reactions (Repeated information provision)" (PSB/ODID Notification No. 0707-3, PSB/SD No. 0707-5, HPB/PD Notification No. 0707-7)
https://www.pmda.go.jp/files/000276266.pdf (only in Japanese)

• Notification dated August 25, 2025 issued jointly by the Director of the Office of Drug Induced Damages at the General Affairs Division and the Director of Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare "Request for Cooperation with the Preparation of Documents, etc. in the Relief System for Adverse Drug Reactions (Information provision)" (PSB/ODID Notification No. 0825-01, PSB/SD No. 0825-01)

• About the establishment of Subcommittee on Evaluation of Adverse Reactions of HPV Vaccines
http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000117420.pdf (only in Japanese)

2

Fire Accidents Involving Patients and Their Families during Use of Long-term Home Oxygen Therapy

1. Introduction

Long-term home oxygen therapy is a treatment that enables patients whose oxygen concentration in the blood decreases to a certain level or lower due to chronic respiratory failure, etc., to inhale oxygen required for living by using an oxygen supply device at home or other places outside the hospital and has been utilized as a treatment for chronic obstructive pulmonary disease (COPD) or interstitial pneumonia that requires long-term oxygen supply. According to the 10th NDB Open Data, the number of cases where long-term home oxygen therapy instruction management fee was claimed per year was 1.92 million, and that of cases where oxygen supply device use fee was claimed per year was 2.44 million[3].

Long-term home oxygen therapy is expected to improve patients' quality of life and reduce their burden associated with hospital visits, and the number of users is on the rise. However, cases of severe disease (burn) and death due to fire accidents during long-term home oxygen therapy have continued to occur. A total of 111 cases were reported in over 21 years from October 2003 to May 2025 (based on the survey of Japan Industrial and Medical Gases Association)[4]. These cases include cases where the cause has not been identified, but there are many reported cases in which the accident was caused by use of fire such as cigarette and gas cooker during the therapy. To date, there have been no reported cases in which outbreak of fire from the oxygen supply device itself was confirmed.

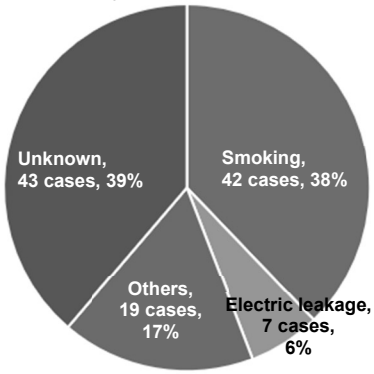
[3] MHLW's the 10th NDB Open Data (based on the numbers for C103 long-term home oxygen therapy instruction management fee, C157 additional fee for oxygen cylinder use, C158 additional fee for oxygen concentrator use, and C159 additional fee for liquid oxygen units use)
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177221_00016.html

[4] A general incorporated association Japan Industrial and Medical Gases Association: Cases of serious health damage due to fire in the houses of patients using long-term home oxygen therapy
https://www.jimga.or.jp/files/page/hot/oyakudachi/HHN_jiko.pdf

Classification by cause of fire accident

* Cases with unknown cause include some cases in which the origin of the fire outbreak is unknown.

* Other causes include stoves, incense sticks, kitchens, and candles.



* Oxygen supply devices have not directly caused a fire.

(Classification by cause of all the 111 cases of fire accident)

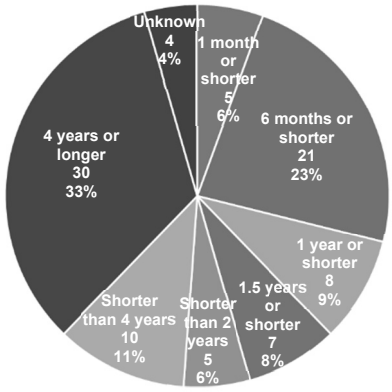
(-) Summarized by the Home Oxygen Subcommittee, Japan Industrial and Medical Gases Association (as of the end of May 2025)

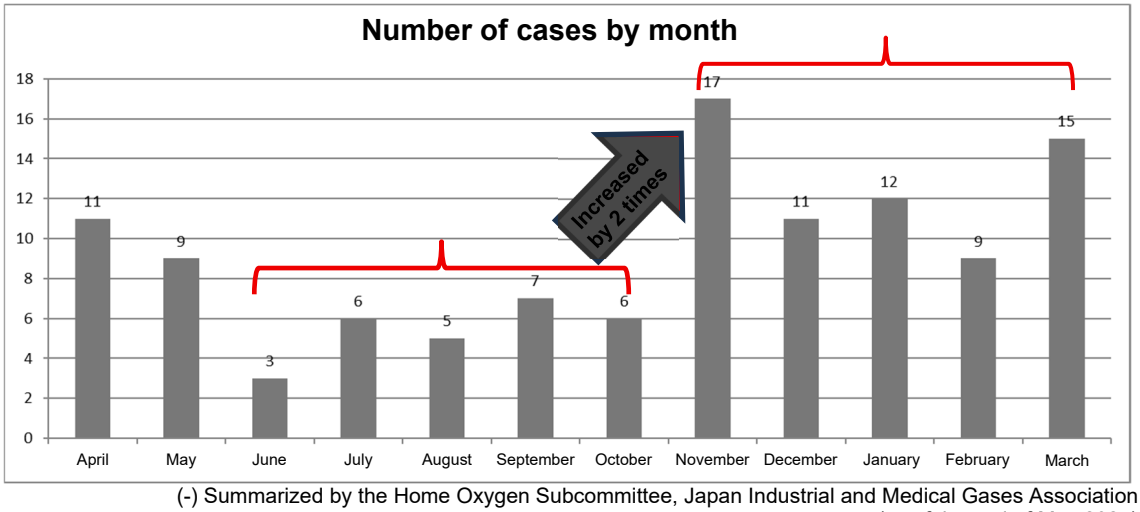
Excerpted from https://www.jimga.or.jp/files/page/hot/oyakudachi/HHN_jiko.pdf

By focusing on the relationship between the duration of long-term home oxygen therapy and the number of cases of fire accident, the trend that beginners who have been receiving the therapy for 6 months or shorter and those who have been receiving the therapy for 4 years or longer account for the high proportion was identified.

By month, the number of cases in November and subsequent months was two times or larger than that in 5 months up to October.

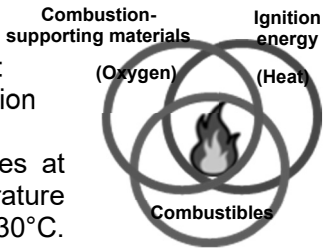
This suggests that it is important to give detailed explanation to patients who start long-term home oxygen therapy as well as continuously give instructions after the introduction and provide precautions when winter has come.





(-) Summarized by the Home Oxygen Subcommittee, Japan Industrial and Medical Gases Association (as of the end of May 2025)

2. Matters That Should Be Explained to Patients Receiving Long-term home oxygen therapy and Their Families, etc.



Fire occurs when the following three components come together: combustibles, oxygen or combustion-supporting materials, and ignition energy (heat).

As a familiar combustible in daily life, the newspaper ignites at 290°C and starts to burn at higher temperature. The ignition temperature of Nylon, a raw material for clothes, is 400°C and that of hair is 230°C. Oxygen inhaled by patients who receive long-term home oxygen therapy is a combustion-supporting gas, and oxygen at high concentrations can cause intense combustion of combustibles.

Meanwhile, the temperature of burning cigarettes is between 700°C and 800°C, and the temperature of electrically heated cigarettes that are recently trending is 350°C or lower, although it varies by the manufacturer. They have energy to ignite combustibles depending on the quality of materials of the combustibles. For an induction cooker, ignition temperatures can be reached when roasting something using it. In other words, heat sources such as heaters may cause a fire even if the flame is not visible. Therefore, they should be handled as fire.

The package inserts and instruction manuals of oxygen supply devices used in long-term home oxygen therapy include a description to the effect that fire should not be used within 2 m around the devices. The relevant organizations and associations have also alerted users (see 4. Reference) and ask healthcare professionals to provide information and give instructions to patients.

However, fire accidents caused by incorrect use of fire by patients using oxygen supply devices have occurred every year. Therefore, healthcare professionals are advised again to thoroughly alert patients receiving long-term home oxygen therapy and their families to use of fire during oxygen inhalation.

1) Putting cigarettes or other materials that can be a source of fire near an oxygen released from an oxygen supply device during oxygen inhalation may cause items such as cannulas and clothing to ignite, resulting in burn injuries or house fires.
2) Never smoke during oxygen inhalation. The same must be applied to electrically heated cigarettes.
3) Any sources of fire (cigarette, heater, stove, gas cooker, candle, incense sticks, matches, lighter, etc.) should not be put within 2 m around oxygen supply devices during use of the devices.
4) For liquid oxygen devices, when liquefied oxygen is transferred from the stationary unit (parent container) to the portable device (child container) to fill the oxygen, fire should not be put within 5 m from the devices.
5) Oxygen will not cause fire when oxygen supply devices are properly used in accordance with the package inserts and appropriate precautions against fire. You are advised to use oxygen therapy in accordance with the instructions given by the doctor without being unduly afraid.

3. Others

Oxygen concentrators, which are used for the vast majority of patients as an oxygen supply device, have been manufactured and marketed in compliance with “JIST7209: 2018 Medical electrical equipment-Particular requirements for basic safety and essential performance of oxygen concentrator equipment” since February 1, 2021.[5] This standard specifies additional requirements for fire prevention and items for reduction of risk of fire caused by accessories, requiring the oxygen outlet connector to be equipped with means to prevent the flame from passing through the connector and entering the inside the device. However, this standard is intended to prevent flame

[5] Japanese Industrial Standard JIST7209: 2018 Medical electrical equipment-Particular requirements for basic safety and essential performance of oxygen concentrator equipment (based on 201.11.2.101 and 201.102.3) https://kikakurui.com/t7/T7209-2018-01.html

from entering inside the device and does not completely prevent fire. Therefore, healthcare professionals are requested to explain the matters described in (2) above to patients receiving long-term home oxygen therapy and their families to cooperate for proper use of oxygen supply devices.

4. References

See information on precautions regarding handling of fire during long-term home oxygen therapy posted on the website of the Ministry of Health, Labour and Welfare.
Handling of fire during long-term home oxygen therapy
https://www.mhlw.go.jp/stf/houdou/2r98520000003m15_1.html (only in Japanese)

The above website also provides links to the following:

- PMDA Medical Safety Information No. 4 “Precautions against smoking and use of fire in Long-term home oxygen therapy” (June 2008)
  https://www.pmda.go.jp/files/000144705.pdf (only in Japanese)
- Joint Notification from the Director of General Affairs Division, Health Policy Bureau, the Director of Guidance Division, Health Policy Bureau, and the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated January 15, 2010 “Handling of fire during Long-term home oxygen therapy (Request for alert and provision of information to users)”
  https://www.mhlw.go.jp/content/11125000/2r98520000003m9w.pdf (only in Japanese)
- Website of a general incorporated association Japan Industrial and Medical Gases Association
  https://www.jimga.or.jp/hot/ (only in Japanese)
  * The following video is also posted:
  “Precautions for handling portable oxygen cylinders”
  https://www.jimga.or.jp/hot/zaitaku_keitai (only in Japanese)
  “Precautions for use of fire in long-term home oxygen therapy”
  https://www.jimga.or.jp/hot/zaitaku_kaki (only in Japanese)

3

Provision of Information on Use of Antipyretic Analgesic During Pregnancy

Acetaminophen is used as a prescription drug and an OTC drug to relieve fever, pain, and inflammation in various diseases.

Some overseas reports suggest that oral administration of acetaminophen affects development of children. However, acetaminophen can be taken during pregnancy as before, and therefore the following questions and answers were added to the “Q&A about Drug during Pregnancy” on the website of the “The Japan Drug Information Institute in Pregnancy” established in the National Center for Child Health and Development.

It is described in the package insert of the prescription drug that acetaminophen preparations can be used if its use is carefully determined, and it has been actually used as the first-choice drug for pain and fever during pregnancy. Therefore, acetaminophen can be taken as before. In the case where patients have any concern about taking the drug, they should consult with their attending physicians or pharmacists as instructed in the Q&A.

Healthcare professionals are encouraged to use this information when responding to inquiries from pregnant women or women who wish to become pregnant.

(Q&A added)
Q. Can I use antipyretic analgesics (drugs for pain or fever) during pregnancy?

A. Acetaminophen is used as the first-choice drug for pain or fever during pregnancy (*). This drug is available in many countries including Europe, UK and Australia (as of October 2025). Some overseas reports suggest that oral administration of acetaminophen affects development of children. However, subsequent large-scale studies in Japan and overseas came to the result that it cannot be said that acetaminophen itself is the cause. Acetaminophen can be taken during pregnancy as before, but if you have any concerns about taking it, consult your doctor or pharmacist.
It is known that other antipyretic analgesics (non-steroidal antipyretic analgesics (e.g., loxoprofen, ibuprofen)) may affect babies when they are used in the second half of pregnancy.

* The package insert of acetaminophen has stated that “acetaminophen should be used during pregnancy only if the expected therapeutic benefits outweigh the possible risks associated with treatment”. Thus, acetaminophen can be administered to pregnant women if its use is carefully determined, and no change has been made to this handling.

If you want to know more:
The Japan Drug Information Institute in Pregnancy is a member of the European Network of Teratology Information Services (ENTIS).
ENTIS provides detailed information about acetaminophen and other antipyretic analgesics.
https://www.entis-org.eu/entis-news/entis-position-statement-paracetamol-in-pregnancy-and-autism-spectrum-disorder

[References]
• “Q&A about Drug during Pregnancy” on the website of the “The Japan Drug Information Institute in Pregnancy” in National Center for Child Health and Development.
https://www.ncchd.go.jp/kusuri/process/qa_ninshin.html (only in Japanese)

• Ministry of Health, Labour and Welfare “Pregnancy and Drugs” page (This page also include explanation on the above Q&A)
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/ninshin_00001.html (only in Japanese)

4

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated October 22,2025, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Lubiprostone

Brand name (name of company)	Amitiza Capsules 12 μg, 24 μg (Viatris Pharmaceuticals Japan G.K.)
Therapeutic category	Purgatives and clysters
Indications	Chronic constipation (excluding constipation due to organic disease)

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS (newly added)	11.1 Clinically Significant Adverse Reactions Anaphylaxis
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving Anaphylaxis reported in Japan: 5 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 1,586,820 Japanese market launch: ［1］ Amitiza Capsules 12 μg :November 2018 ［2］ Amitiza Capsules 24 μg :November 2012

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 50s	Constipation (osteoporosis, lumbago)	24 μg 1 day (once) ↓ Discontinuation	**Shock**	
				Day 1 of administration (day of discontinuation)	Lubiprostone was initiated.
				Approximately 10 minutes after administration	The patient experienced symptoms including the following: Sensation of sputum in the throat, dry cough with gradually shortened intervals that prevented deep breaths and a feeling of a puffy face; while checking her face in the mirror, her vision gradually whitened, and she became unable to stand. Blood pressure: 74 mmHg. It was judged that pharyngolaryngeal oedema occurred, and an intravenous infusion of betamethasone sodium phosphate was started. Lubiprostone was discontinued.
				2 hours after administration	The patient recovered.
	Concomitant drugs: Magnesium oxide, eldecalcitol				

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 50s	Constipation (Systemic lupus erythematosus, multiple microinfarctions, convulsive seizure, sleeplessness, persecutory delusion, auditory hallucination)	24 μg 1 day (once) ↓ Discontinuation	**Shock** Allergy history: None	
				Day 1 of administration (day of discontinuation)	Blood pressure: 133/91 mmHg. Lubiprostone was initiated.
				1 hour 12 minutes after administration	The patient had facial pallor and cold sweat. HR at 55 - <60. Blood pressure: 50/38 mmHg. Lubiprostone was discontinued.
				1 hour 28 minutes after administration	Blood pressure: 63/45 mmHg. Flushing with 3 mL of noradrenaline before starting it at 2 mL/hr. Subsequently, administration was adjusted in accordance with the order sheet.
				1 hour 32 minutes after administration	HR decreased to 44.
				1 hour 36 minutes after administration	HR spontaneously recovered to 60 - <70. Intravenous *d*-chlorpheniramine maleate 2 mg was injected.
				2 hours 7 minutes after administration	Intravenous hydrocortisone sodium succinate 100 mg was infused.
				3 hours 48 minutes after administration	Echocardiography confirmed no problem.
				2 days after discontinuation	It was switched to a combination drug of macrogol 4000, sodium chloride, sodium bicarbonate, and potassium chloride.
				3 days after discontinuation	Noradrenaline was discontinued. Blood pressure: 104/77 mmHg.

Laboratory test value

Test items (unit)	Day 1 of administration	1 hour 12 minutes after administration	1 hour 28 minutes after administration	1 hour 32 minutes after administration	1 hour 36 minutes after administration	3 days after discontinuation
Blood pressure (mmHg)	133/91	50/38	63/45	–	–	104/77
Heart rate (bpm)	–	55 to 59	–	44	60 to 69	–

Concomitant drugs: Prednisolone, esomeprazole magnesium hydrate, Aspirin, mycophenolate mofetil, sulfamethoxazole/trimethoprim, levetiracetam, suvorexant, alendronate sodium hydrate, trazodone hydrochloride, lacosamide, quetiapine fumarate, risperidone

5

Revisions of PRECAUTIONS (No. 364)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated October 22, 2025.

1 Purgatives and clysters

Lubiprostone

Brand name
Amitiza Capsules 12 μg, 24 μg (Viatris Pharmaceuticals Japan G.K.)

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

2 Estrogen and progestogen preparations, mixed hormone preparations

[1] Estradiol (oral dosage form)
[2] Estradiol valerate
[3] Estriol (oral dosage form)
[4] Progesterone (oral dosage form)
[5] Estradiol/Norethisterone acetate
[6] Estradiol/Levonorgestrel
[7] Testosterone enanthate/Estradiol valerate

Brand name
[1] Julina tablets 0.5 mg, etc. (Bayer Yakuhin, Ltd., etc.)
[2] Progynon-Depot intramuscular injection 10 mg (Fuji Pharma Co., Ltd.), Pelanin depot Intramuscular Injection 5 mg, 10 mg (Mochida Pharmaceutical Co., Ltd.)
[3] Estriel Tablets 100γ, 0.5 mg, 1 mg, etc. (Mochida Pharmaceutical Co., Ltd., etc.), Holin Tablets 1 mg (Aska Pharmaceutical Co., Ltd.), Estriel Vaginal Tablets 0.5 mg (Mochida Pharmaceutical Co., Ltd.), Holin V Vaginal Tablets 1 mg (Aska Pharmaceutical Co., Ltd.)
[4] F-meno capsules 100 mg (Fuji Pharma Co., Ltd.)
[5] Menoaidcombi Patches (Hisamitsu Pharmaceutical Co., Inc.)
[6] Wellnara combination tablets (Bayer Yakuhin, Ltd.)
[7] Primodian-Depot intramuscular injection, etc. (Fuji Pharma Co., Ltd., etc.)

15. OTHER PRECAUTIONS
HRT and risk of breast cancer

15.1 Information Based on Clinical Use (newly added)
The causal relationship between HRT and breast cancer development is not clear, but the following reports have been made.
A meta-analysis of large-scale epidemiological studies in postmenopausal women showed that the risk of breast cancer was increased with the duration of menopausal hormone replacement therapy (MHT) in women treated with estrogen alone or in combination with estrogen and gestagen preparations as

	MHT (adjusted risk ratio [95% confidence interval], 1.60 [1.52 to 1.69] for the combination of estrogen and gestagen preparations for 1 to 4 years, 1.17 [1.10 to 1.26] for estrogen alone, 2.08 [2.02 to 2.15] for combination of estrogen and gestagen preparations for 5 to 14 years, and 1.33 [1.28 to 1.37] for estrogen alone), with the MHT non-users-adjusted risk ratio being higher in current MHT users than in prior MHT users. In addition, it has been reported that the risk of breast cancer may persist for 10 years or more in prior MHT users, depending on the duration of previous treatment, even after discontinuation.

3 Estrogen and progestogen preparations

[1] Estradiol (preparations for cutaneous application)
[2] Estrogens, conjugated

Brand name	[1] Estrana Tapes 0.09 mg, 0.18 mg, 0.36 mg, 0.72 mg (Hisamitsu Pharmaceutical Co., Inc.), Divigel 1 mg (Orion Pharma Japan K.K.), L'estrogel 0.06% (Fuji Pharma Co., Ltd.) [2] Premarin Tablets 0.625 mg (Pfizer Japan Inc.)
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use (newly added)**	HRT and risk of breast cancer The causal relationship between HRT and breast cancer development is not clear, but the following reports have been made. A meta-analysis of large-scale epidemiological studies in postmenopausal women showed that the risk of breast cancer increased with the duration of menopausal hormone replacement therapy (MHT) in women treated with estrogen alone or in combination with estrogen and gestagen preparations as MHT (adjusted risk ratio [95% confidence interval], 1.60 [1.52 to 1.69] for the combination of estrogen and gestagen preparations for 1 to 4 years, 1.17 [1.10 to 1.26] for estrogen alone, 2.08 [2.02 to 2.15] for combination of estrogen and gestagen preparations for 5 to 14 years, and 1.33 [1.28 to 1.37] for estrogen alone), with the MHT non-users-adjusted risk ratio being higher in current MHT users than in prior MHT users. In addition, it has been reported that the risk of breast cancer may persist for 10 years or more in prior MHT users, depending on the duration of previous treatment, even after discontinuation.
	(Deleted)

4 Vaccines

Freeze-dried recombinant herpes zoster vaccine (prepared from Chinese hamster ovary cells)

Brand name	Shingrix intramuscular injection (GlaxoSmithKline K.K.)
11. Adverse Reaction **11.1 Clinically Significant Adverse Reactions (newly added)**	Guillain-Barré Syndrome Symptoms such as flaccid paralysis starting from the distal limbs and decreased or absent tendon reflexes may occur.

6

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 September 30, 2025)
◎: Products for which EPPV was initiated after September 1, 2025

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
◎	Coronavirus (SARS-CoV-2) RNA Vaccine DAICHIRONA INTRAMUSCULAR INJECTION	Daiichi Sankyo Co., Ltd.	September 19, 2025
◎	Etrasimod L-Arginine Velsipity Tablets 2 mg	Pfizer Japan Inc.	September 12, 2025
	Miglustat[*1] Opfolda Capsules 65 mg	Amicus Therapeutics, Inc.	August 27, 2025
	Cipaglucosidase alfa (genetical recombination) Pombiliti for I.V. Infusion 105 mg	Amicus Therapeutics, Inc.	August 27, 2025
	Recombinant adsorbed 9-valent human papillomavirus virus-like particle vaccine (yeast origin)[*2] Silgard 9 Aqueous Suspension for Intramuscular Injection Syringes	MSD K.K.	August 25, 2025
	Selumetinib Sulfate Koselugo Capsules 10 mg, 25 mg	Alexion Pharma Godo Kaisha	August 25, 2025
	Avatrombopag Maleate[*3] Doptelet tablets 20 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	August 25, 2025
	Belzutifan Welireg Tablets 40 mg	MSD K.K.	August 18, 2025
	Sotatercept (genetical recombination) Airwin for Subcutaneous Injection 45 mg, 60 mg	MSD K.K.	August 18, 2025
	Talquetamab (genetical recombination)	Janssen	August 14, 2025

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
	Talvey Subcutaneous Injection 3 mg, 40 mg	Pharmaceutical K.K.	
	Erdafitinib Balversa Tablets 3 mg, 4 mg, 5 mg	Janssen Pharmaceutical K.K.	July 16, 2025
	Tislelizumab (genetical recombination) Tevimbra I.V. Infusion 100 mg	BeOne Medicines Japan	July 1, 2025
	Drospirenone[*4] Slinda 28 Tablets	Aska Pharmaceutical Co., Ltd.	June 30, 2025
	Purified Vi polysaccharide typhoid vaccine Typhim Vi Syringe for Injection	Sanofi K.K.	June 30, 2025
	Guselkumab (genetical recombination)[*5] Tremfya Intravenous Infusion 200 mg, Tremfya Subcutaneous Injection Syringe 100 mg, 200 mg, Tremfya Subcutaneous Injection 200 mg Pen	Janssen Pharmaceutical K.K.	June 24, 2025
	Vutrisiran sodium[*6] Amvuttra Subcutaneous Injection 25 mg Syringe	Alnylam Japan K.K.	June 24, 2025
	pH4-Treated acidic normal human immunoglobulin (subcutaneous injection), vorhyaluronidase alfa (genetical recombination)[*7] HyQvia 10% S.C. Injection Set 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	Takeda Pharmaceutical Company Limited	June 24, 2025
	IncobotulinumtoxinA Xeomin 50 units, 100 units, 200 units for injection	Teijin Pharma Limited	June 24, 2025
	Remimazolam besilate[*8] Anerem 50 mg for I.V. Injection	Mundipharma K.K.	June 24, 2025
	Maralixibat chloride Livmarli Oral Solution 10 mg/mL	Takeda Pharmaceutical Company Limited	June 12, 2025
	pH4-Treated acidic normal human immunoglobulin (subcutaneous injection), vorhyaluronidase alfa (genetical recombination) HyQvia 10% S.C. Injection Set 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	Takeda Pharmaceutical Company Limited	June 12, 2025
	Ivosidenib Tibsovo Tablets 250 mg	Nihon Servier Co., Ltd.	June 2, 2025
	Amivantamab (genetical recombination)[*9] Rybrevant Intravenous Infusion 350 mg	Janssen Pharmaceutical K.K.	May 21, 2025
	Tisotumab vedotin (genetical recombination)	Genmab K.K.	May 21, 2025

Nonproprietary name Brand name		Name of the MAH	Date of EPPV initiation
	Tivdak for Intravenous Infusion 40 mg		
	Lazertinib mesilate hydrate Lazcluze Tablets 80 mg, 240 mg	Janssen Pharmaceutical K.K.	May 21, 2025
	Guselkumab (genetical recombination)*10 Tremfya Intravenous Infusion 200 mg, Tremfya Subcutaneous Injection 200 mg Syringe, 200 mg Pen, 100 mg Syringe	Janssen Pharmaceutical K.K.	May 21, 2025
	Mavacamten Camzyos capsules 5 mg, 2.5 mg, 1 mg	Bristol-Myers Squibb K.K.	May 21, 2025
	Acoramidis hydrochloride Beyonttra tablets 400 mg	Alexion Pharma Godo Kaisha	May 21, 2025
	Amivantamab (genetical recombination)*11 Rybrevant Intravenous Infusion 350 mg	Janssen Pharmaceutical K.K.	May 19, 2025
	Iptacopan hydrochloride hydrate*12 Fabhalta capsules 200 mg	Novartis Pharma K.K.	May 19, 2025
	Atropine sulfate hydrate*13 Ryjusea Mini ophthalmic solution 0.025%	Santen Pharmaceutical Co., Ltd.	April 21, 2025
	Garadacimab (genetical recombination) Andembry S.C. Injection 200 mg Pens	CSL Behring K.K.	April 18, 2025
	Brivaracetam Briviact for I.V. injection 25 mg	UCB Japan Co. Ltd.	April 17, 2025
	Tarlatamab (genetical recombination) Imdelltra For I.V. Infusion 1 mg, 10 mg	Amgen K.K.	April 16, 2025
	Tirzepatide*14 Zepbound Subcutaneous Injection Ateos 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Eli Lilly Japan K.K.	April 11,2025

*1 Combination therapy with cipaglucosidase alfa (genetical recombination) for late onset pompe's disease

*2 Prevention of the following diseases caused by infection with human papillomavirus types 6, 11, 16, 18, 31, 33, 45, 52, and 58
• Anal cancer (squamous cell carcinoma) and its precursor lesions (anal intraepithelial neoplasia (AIN) grades 1, 2, and 3)

*3 Persistent and chronic immune thrombocytopenia

*4 Contraception

*5 Treatment of moderate to severe active Crohn's disease (only in patients who have had an inadequate response to conventional treatments)

*6 Transthyretin cardiac amyloidosis (wild type and mutant type)

*7 Slowing the progression of motor function decline in chronic inflammatory demyelinating polyradiculoneuritis and multifocal motor neuropathy (when improvement in muscle weakness is observed)

*8 Sedation during gastrointestinal endoscopy

*9 Coadministration with lazertinib mesilate hydrate for unresectable, advanced or recurrent *EGFR* mutation-positive non-small cell lung cancer

*10 Maintenance therapy for moderate to severe ulcerative colitis (only in patients who have had an inadequate response to conventional treatments)

*11 Coadministration with carboplatin and pemetrexed sodium hydrate for unresectable, advanced or recurrent *EGFR* mutation-positive non-small cell lung cancer

*12 C3 nephropathy

*13 Slowing the progression of myopia

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.

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