# Pharmaceuticals and Medical Devices Safety Information

## No. 415 December 2024

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) web page (https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html) and on the MHLW website (https://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

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

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

Register here


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# Pharmaceuticals and Medical Devices Safety Information

**No. 415 December 2024**

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


## [ Outline of Information ]



*E:* Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of PRECAUTIONS, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of healthcare professionals.

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

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

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

This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

## Abbreviations

| | |
|---|---|
| ADEM | Acute Disseminated Encephalomyelitis |
| ADR | Adverse Drug Reaction |
| DIHS | Drug-Induced Hypersensitivity Syndrome |
| EPPV | Early Post-marketing Phase Vigilance |
| FY | Fiscal Year |
| GAD | General Affairs Division |
| HHV-6 | Human Herpes Virus type 6 |
| HPV | Human Papilloma Virus |
| HSB | Health Service Bureau |
| MAH | Marketing Authorization Holder |
| MEXT | Ministry of Education, Culture, Sports, Science and Technology |
| MHLW | Ministry of Health, Labour and Welfare |
| ODID | Office of Drug Induced Damages |
| OTC | Over-the-Counter |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PSEHB | Pharmaceutical Safety and Environmental Health Bureau |
| RS | Respiratory Syncytial |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SD | Safety Division |
| SYB | Sports and Youth Bureau |

# 1

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

## 1. Introduction

The Relief System for Adverse Drug Reactions (ADRs)[1] (hereinafter referred to as "the Relief System") was established in 1980 to bring prompt relief to people who suffer from adverse health effects such as disorders or disabilities caused by adverse reactions to drugs despite their proper use. This is a public service funded by contributions from marketing authorization holders (MAHs) of drugs, etc. as a way to fulfill some of 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 suffer from adverse health effects such as disorders or disabilities caused by viral infections, etc. acquired through the use of biological products despite their proper use. Furthermore, adverse reactions to regenerative medical products and infections, etc. acquired through the use of such products have been covered by the relief systems since 2014.

Adverse health effects caused by vaccination (routine vaccination and temporary vaccination, etc.) under the Preventative Vaccination Law are not covered by the Relief System, but by the Relief System for Injury to Health With Vaccination Under the Preventative Vaccination Law. On the other hand, adverse health effects caused by voluntary vaccinations are eligible for relief under the Relief System or the Relief System for Infections Derived From Biological Products.

COVID-19 vaccination, which was conducted as a special temporary vaccination until March 31, 2024, has been classified as a routine vaccination for category B diseases since April 1, 2024 under the Preventative Vaccination Law for (1) elderly persons aged 65 years or older, and (2) persons aged 60 years to 64 years who have disabilities in heart, kidney, or respiratory function, causing significant limitations in daily life activities, or who have immune function disabilities due to human immunodeficiency virus, making daily life activities nearly impossible. On the other hand, it was decided that the opportunities were to be ensured as a voluntary vaccination for other people as well. Therefore, please note that the relief system under which a claim should be made differs depending on the date of vaccination and the types of vaccination. For the details, please refer to "Handling of Relief Measures for Adverse Health Effects Caused by COVID-19 Vaccination Since 2024" (Joint Administrative Notice issued by the Vaccination Division, Department of Infectious Disease Prevention and Control, Public Health Bureau and Office of Drug-Induced Damages, General Affairs Division, Pharmaceutical Safety Bureau, MHLW, dated March 11, 2024)[2].

Under the Relief System, a total of 30,254 cases have been granted relief benefits since its establishment in 1980 until the end of fiscal year (FY) 2023. People who have suffered from adverse health effects associated with adverse reactions more often obtain information on the Relief System from healthcare professionals such as physicians and pharmacists. Healthcare professionals are requested to provide information on the Relief System and cooperate with the preparation of medical certificates, etc. required for claiming relief benefits.

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[1] About the Relief System (PMDA website):
https://www.pmda.go.jp/relief-services/outline/0001.html (in Japanese),
https://www.pmda.go.jp/english/relief-services/0002.html (in English)
For the forms of necessary documents for making claims:
https://www.pmda.go.jp/relief-services/adr-sufferers/0004.html (only in Japanese)

[2] Administrative Notice: https://www.mhlw.go.jp/content/001223621.pdf (only in Japanese)

## 2. Adverse health effects eligible for the Relief System

Adverse health effects eligible for the Relief System include disorders (severe enough to require hospital admission), disabilities (severe enough to significantly limit daily life activities), and deaths despite the proper use of drugs or regenerative medical products.

Drugs, etc. eligible for the Relief System include those prescribed or used at hospitals and clinics as well as those purchased at pharmacies, etc.; however, some drugs, such as anticancer drugs and immunosuppressants, are excluded from the Relief System. In addition, claims for medical expenses for disorders, etc. have a deadline, and claims for eligible payments of medical expenses must be submitted within 5 years after such expenses have been paid.

[Types and amounts of relief benefits (as of April 1, 2024)]
Medical expenses (costs borne by the patients, not including health insurance payments)
• Actual costs of treatment for the disease caused by ADRs will be compensated.
Medical allowance (36,900 to 38,900 yen per month)
• Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs.
Disability pension (Grade 1: 2,966,400 yen per year, Grade 2: 2,373,600 yen per year)
• Benefits are provided to compensate for living costs, etc. of patients aged 18 years or older, who suffer from a certain degree of disability caused by ADRs.
Pension for raising children with disabilities (Grade 1: 927,600 yen per year, Grade 2: 741,600 yen per year)
• Benefits are provided to people who are responsible for raising children under 18 years who suffer from a certain degree of disability caused by ADRs.
Bereaved family pension (2,594,400 yen)
• Benefits are provided for bereaved families to rebuild their lives following the deaths of their main providers from ADRs.
Lump-sum benefits for bereaved families (7,783,200 yen)
•Benefits are provided to bereaved families for condolence and sympathy following the death due to ADRs of a family member who is not the main provider.
Funeral expenses (215,000 yen)
• Benefits are provided for the costs of holding a funeral for people who died of ADRs.

## 3. Awareness of the Relief System

Awareness of the Relief System among the general public in FY 2023 was 32.8% in total according to the FY 2023 survey: 11.1% answered that they “were aware” of the Relief System and 21.7% 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 that they have suffered because they are unaware of the Relief System.

On the other hand, the awareness among healthcare professionals was 84.3% in total: 62.0% answered that they “were aware” of the Relief System and 22.3% answered that they “have heard about” the Relief System. By occupational category, awareness was 91.0% among physicians, 96.8% among pharmacists, 65.7% among nurses, and 83.2% among dentists. Among the healthcare professionals who were aware of the Relief System, the proportion of those who had been involved in a filing procedure was 11.6% overall: 15.1% among physicians, 12.0% among pharmacists, 7.9% among nurses, and 8.9% among dentists. [Note 1)]

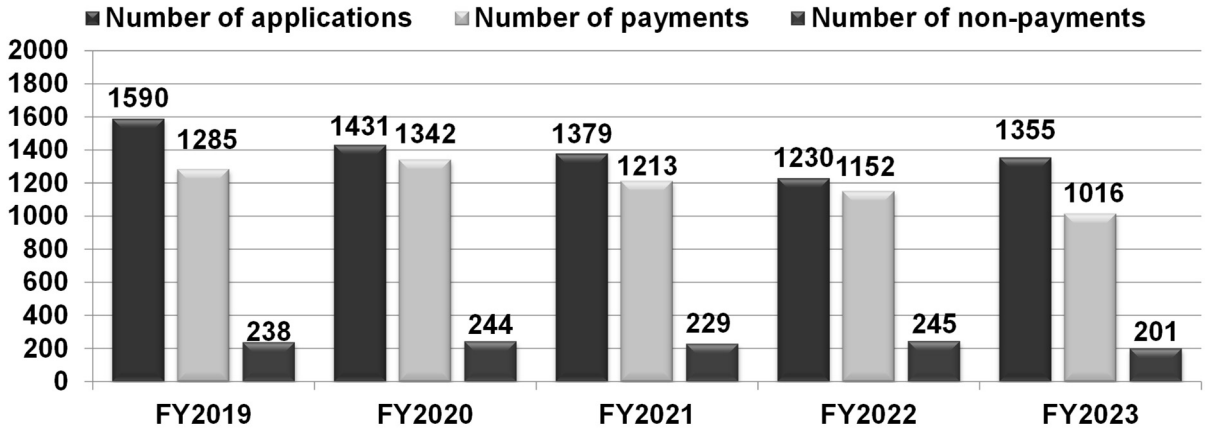
Furthermore, in all application forms related to relief benefits, the input field for “the source of information related to the Relief System” (selected from “Physician,” “Dentist,” “Pharmacist,” “Other medical facility staff,” “Newspaper/TV, etc.” and “Others”) was newly included in April 2016 to identify the sources of information related to the Relief System. The FY 2023 results showed “Physician” in 438 answers (30.6%), “Others” (the Internet) in 282 answers (19.7%), “Pharmacist” in 145 answers (10.1%) in descending order (multiple answers acceptable). [Note 1)]

## 4. Status of payment/non-payment cases in the Relief System

The annual numbers of applications and payments in the Relief System between FY 2019 and FY 2023 are shown in Figure 1. In FY 2023, the number of applications was 1,355, the number of payments was 1,016, and the number of non-payments was 201. The ratios between payment and non-payment and details of reasons for non-payments from FY 2019 to FY 2023 are shown in Figure 2.

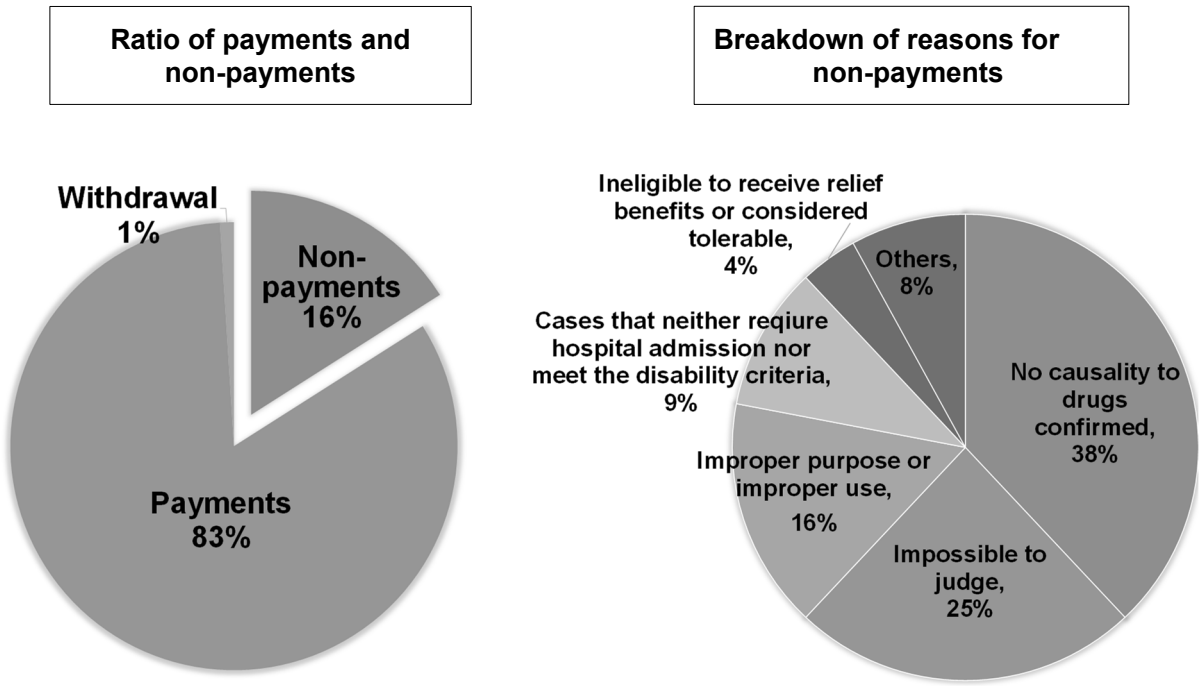
In addition, the standard administrative processing time [Note 2)] from when the PMDA receives an application to when the PMDA notifies the applicant of the decision is 6 months or less. The goal is to achieve the standard administrative processing time in 65% or more of cases (60% or more until FY2022), for which payment or non-payment was determined. The actual achievement percentage in FY 2023 was 92.1%, which was the highest result greatly exceeding 65%.

**Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2019 to FY 2023)**




(Graph description)
*The number of cases is applicant-based. If a second claim is made for the same cause after the first, the 2 applications are counted as 1 case.
*Since it requires a certain period of time from the acceptance of a claim to the judgment to provide relief benefits, the number of claims does not correspond to the total number of payments and non-payments within the same fiscal year.

**Figure 2 Ratio of payments and non-payments and breakdown of reasons for non-payments between FY 2019 and FY 2023**




## 5. Cases of relief benefit payments/non-payments

### 5.1 Cases of relief benefit payments

<Case 1> A case of acute disseminated encephalomyelitis (ADEM) due to an influenza vaccine, for which medical expenses and medical allowance benefits were provided

A female in her 30s. She developed ADEM following influenza vaccination and received inpatient treatment. Medical expenses and medical allowance benefits were provided.

<Case 2> A case of anaphylactic shock due to iopamidol, for which medical expenses, medical allowance, lump-sum benefits for bereaved family members, and funeral expenses benefits were provided

A female in her 70s. The patient died due to anaphylactic shock after using iopamidol. Medical expenses, medical allowance benefits, lump-sum benefits for bereaved family members, and funeral expenses benefits were provided.

<Case 3> A case of cerebral haemorrhage due to clopidogrel and the resulting functional disorder in the extremities, higher brain dysfunction, mastication disorder/swallowing dysfunction, and language disorder, which led to a disability status, for which medical expenses, medical allowance benefits, and disability pension benefits were provided

A female in her 80s. She experienced cerebral haemorrhage following the use of clopidogrel and received inpatient treatment. She had functional disorder in the extremities, higher brain dysfunction, mastication disorder/swallowing dysfunction, and language disorder due to cerebral haemorrhage. Medical expenses, medical allowance, and disability pension benefits were provided.

<Case 4> A case of erythema multiforme-type drug eruption due to an over-the-counter (OTC) drug, for which medical expenses and medical allowance benefits were provided

A female in her 30s. She experienced erythema multiforme type drug eruption following the use

of Bufferin Premium and received inpatient treatment. Medical expenses and medical allowance benefits were provided.

**5.2 Cases of relief benefit non-payments (cases in which the method of use of the drug was not considered proper)**

Of the 1,157[Note 3)] non-payment cases from FY 2019 to FY 2023, the reason for non-payment in approximately 16% of them was that the purpose or method of use of the drug was not considered proper (Figure 2). Table 1 shows the most common drugs for which the method of use, etc. was not considered proper.

Among the cases in which relief benefits have not been approved, the cases for which the method of use, etc. was not considered proper most recently (in the last year or so) are introduced in this section.

**Table 1. Number of cases in which the method, etc. of use of the drug was not considered proper (FY 2019 to FY 2023)**

| Name of causative drug | FY2019 | FY2020 | FY2021 | FY2022 | FY2023 | Total (cases) |
|---|---|---|---|---|---|---|
| Lamotrigine | 15 | 8 | 5 | 3 | 12 | 43 |
| Human chorionic gonadotrophin | 1 | 2 | 4 | 5 | 5 | 17 |
| Methotrexate | 4 | 5 | 1 | 0 | 2 | 12 |
| Thiamazole | 2 | 4 | 2 | 0 | 3 | 11 |
| Lithium carbonate | 3 | 0 | 3 | 4 | 0 | 10 |
| Others | 21 | 16 | 22 | 21 | 18 | 98 |
| Total (cases) | 46 | 35 | 37 | 33 | 40 | 191 |

**(1) Cases where the drug was used without adhering to the approved dosage and administration**

Lamotrigine accounts for the majority of the cases where the drug was used without adhering to 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 the drug.

**<Case 1> A case of drug-induced hypersensitivity syndrome (DIHS) due to lamotrigine (during titration period)**

A female in her 40s. She used lamotrigine for epilepsy. In monotherapy, lamotrigine was started from a daily dose of 25 mg, which was increased to 50 mg/day after 7 days. Therefore, this drug use was not considered proper.

**<Case 2> A case of erythema multiforme-type drug eruption due to lamotrigine (when initiating administration)**

A female in her 30s. She used lamotrigine for bipolar disorder. In monotherapy, lamotrigine was started from a daily dose of 50 mg as the first dose. Therefore, this drug use was not considered proper.

<u>Improper use of lamotrigine</u>

It has been demonstrated in a clinical study conducted in Japan that the incidence of skin disorders is high when lamotrigine is administered at a dose exceeding the approved dosage and administration, and there has been an alert since the approval of Lamictal Tablets in October 2008 to adhere to the specified dosage and administration. However, severe skin disorders have continued to be reported, and the PMDA issued the Alert for Proper Use of Drugs in January 2012 [Note 4)] and the Dear Healthcare Professional Letter of Rapid Safety Communication (Blue Letter) in February 2015, for example, to alert healthcare professionals in various ways to adhere to the approved dosage and administration, including the dosage when initiating administration and the

dosage when titrating, as well as alternate-day administration and the timing of titration.

Despite such precautions, there have been many cases of patients who file an application for compensation for ADRs but fail to receive the relief benefit payments because they are not accepted as proper use. The PMDA issued the Alert for Proper Use of Drugs in October 2019 [Note 5)] as a reminder of required caution.

Many of these cases in which a payment was not approved due to improper use were associated with a prescription of excessive doses at the start of administration or during titration up to the maintenance dose, or a dose escalation ahead of schedule.

Dosage and administration of lamotrigine are closely regulated in terms of dosage and dose increase intervals depending on the specific indications and concomitant drugs. Dosage and administration when used for suppression of recurrent/relapsed mood episodes in bipolar disorder in adults stated in the electronic package insert of the original drug (Lamictal) are shown below as an example. Please make sure to read the latest electronic package insert carefully before use, including other dosage and administration details.

**Descriptions in the electronic package insert of Lamictal Tablets (lamotrigine)(revised in February 2022) (partial excerpt)**

When used for suppression of recurrent/relapsed mood episodes in bipolar disorder (adult)

| | Concomitant medication | | | |
|---|---|---|---|---|
| Concomitant drugs with lamotrigine | (2) With sodium valproate | (3) Without sodium valproate*1 | | (1) Lamotrigine monotherapy |
| | | (3)-i) With drugs that induce glucuronidation of lamotrigine*2 | (3)-ii) With drugs other than (3)-i)*3 | |
| Week 1/2 | 25 mg/day every 2 days | 50 mg/day (once daily) | 25 mg/day (once daily) | |
| Week 3/4 | 25 mg/day (once daily) | 100 mg/day (twice daily in divided doses) | 50 mg/day (once or twice daily in divided doses) | |
| Week 5 | 50 mg/day (once or twice daily in divided doses) | 200 mg/day (twice daily in divided doses) | 100 mg/day (once or twice daily in divided doses) | |
| After Week 6 | 100 mg/day (maximum 200 mg/day) (once or twice daily in divided doses) (Dose should be increased by up to 50 mg/day with an interval of 1 week or longer.) | Week 6 300 mg/day, week 7 and after 300 mg/day to 400 mg/day (maximum 400 mg/day) (twice in divided doses daily) (Dose should be increased by up to 100 mg/day with an interval of 1 week or longer.) | 200 mg/day (maximum 400 mg/day) (once or twice daily in divided doses) (Dose should be increased by up to 100 mg/day with an interval of 1 week or longer.) | |

Lamotrigine is mainly metabolized by glucuronyl transferase.

*1) In combination therapy with drugs whose effects on the glucuronidation of this drug are not

known, the dosage and administration for concomitant use with sodium valproate should be followed.
*2) Drugs that induce glucuronidation of lamotrigine: Phenytoin, carbamazepine, phenobarbital, primidone, rifampicin, lopinavir/ritonavir combination agents
*3) Drugs that have no effect on the glucuronidation of lamotrigine: Aripiprazole, olanzapine, zonisamide, gabapentin, cimetidine, topiramate, pregabalin, lithium, levetiracetam, perampanel, lacosamide

**(2) Cases where the required tests were not conducted**

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

To detect ADRs early and prevent them from becoming serious, it is considered necessary to perform appropriate tests and provide explanations about the necessity of tests in a way that patients can understand. Thus, healthcare professionals are strongly advised to read through the electronic package insert once again.

**<Case 1> A case of lithium poisoning due to lithium carbonate**

A female in her 60s. Since no serum lithium level had been measured for approximately 7 months until lithium poisoning was observed after the patient took lithium carbonate with the maintenance dose, the case was not approved as proper use.

**Description in the electronic package insert of Lithium Carbonate Tablets 100 mg "Amel" (revised in November 2024)** (partial excerpt)

[PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION]

Lithium poisoning may occur as a result of an overdose. The serum lithium level should be measured approximately once weekly at the initial phase of administration or when the dose is increased until the maintenance dose is fixed, and at least once approximately 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 serum 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.

<u>Tests not conducted when using lithium carbonate</u>

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 the PMDA and various materials, but cases where tests were not conducted have still been reported.

**<Case 2> A case of agranulocytosis due to thiamazole**

A female in her 40s. Since no blood tests including differential count of leukocytes had been conducted for 34 days until agranulocytosis was observed during thiamazole administration, the case was not approved as proper use.

**Description in the electronic package insert of Mercazole Tablets (thiamazole)(revised in June 2022)** (partial excerpt)

[WARNINGS]

Serious agranulocytosis has been reported especially within the first 2 months after initiating administration, leading to fatal outcomes in some cases. In principle, a blood test including differential count of leukocytes should be conducted once every 2 weeks for at least 2 months after the start of administration and periodically thereafter. When any abnormalities such as decreasing tendency of granulocytes are observed, administration should be discontinued

immediately and appropriate measures should be taken. Similar caution is required when administration of the drug is resumed after its discontinuation.

**(3) Cases where patients used drugs at their own discretion and not by physicians' instructions**

In cases where patients used drugs prescribed by physicians at their own discretion ignoring physicians' instructions, or patients used drugs that were prescribed for their family members or acquaintances, not for themselves, such uses will not be considered proper.

Healthcare professionals should provide definite instructions, such as specific ones regarding dosing days, dosing conditions, and doses so that patients can manage their drugs appropriately.

**<Case> A case of oculomucocutaneous syndrome (Stevens-Johnson syndrome) due to loxoprofen**

A female in her 30s. As a result of taking loxoprofen sodium for pyrexia/pharyngodynia, the occurrence of oculomucocutaneous syndrome (Stevens-Johnson syndrome) was noted. Since the patient took the unused drugs that were prescribed for her family members at her own discretion ignoring the physician's instruction, the case was not approved as proper use.

**(4) Cases of use in patients falling under the CONTRAINDICATIONS**

There are also cases where the drug was used in patients falling under the CONTRAINDICATIONS and the use was not considered proper.

Healthcare professionals are strongly advised to use drugs properly considering the conditions of the patients who are using the drug and the contraindications of the drug being used.

**<Case> A case in which miconazole was used in patients taking warfarin**

A female in her 40s. While she was receiving treatment with warfarin potassium, miconazole, whose co-administration is contraindicated, was used. She developed marked coagulopathy, which was prolonged due to interactions, and purpura developed across her entire body. The case was not approved as proper use based on the clinical course.

**Description in the electronic package insert of Warfarin tablets (warfarin potassium) (revised in November 2023)** (partial excerpt)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
   2.10 Patients receiving miconazole (gels/injections/tablets)
10. INTERACTIONS
   10.1 Contraindications for Co-administration
   Miconazole (gels/injections/tablets) (Florid Oral Gel, Florid-F Injection, Oravi Mucoadhesive Tablets): The effects of this drug may be enhanced. Also, some cases have been reported in which the effect of this drug was prolonged even after discontinuation of co-administration of miconazole, leading to haemorrhage and increased INR. If the patient requires the treatment with this drug, treatment with this drug should be prioritized and miconazole (gels/injections/tablets) should not be administered.

Healthcare professionals should reconfirm the descriptions in the electronic package inserts for proper use of the drugs.

PMDA Alert for Proper Use of Drugs

https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/properly-use-alert/0003.html (in Japanese)

https://www.pmda.go.jp/english/safety/info-services/drugs/properly-use-alert/0001.html (in English)

## 6. Source of information on the Relief System

Details of the Relief System as well as the Relief System for Infections Derived from Biological Products can be found on the PMDA's website (http://www.pmda.go.jp/relief-services/index.html (only in Japanese)). 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 system.

The forms of necessary documents for making claims can be downloaded from the following webpages, and documents can be created electronically using a personal computer, etc. If the documents are created electronically using a personal computer, etc., claimants are requested to submit paper-based documents as well as to 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 (only in Japanese)
The Relief System for Infections Derived from Biological Products
https://www.pmda.go.jp/relief-services/infections/0007.html (only in Japanese)

Details of medical certificates and certificates for prescription/use are important information when judging whether the use was proper or not, 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 receiving relief benefits.

A. Cases of adverse health effects caused by statutory vaccination practice (Relief System for Injury to Health with Vaccination is applicable under the Preventative Vaccination Law.) However, cases of adverse health effects caused by voluntary vaccinations are eligible for relief benefits under the Relief System.
B. Cases in which it is clear who else is liable for the damages such as MAHs [Note 6)]
C. Cases of adverse health effects as a result of using the drug in an amount exceeding the approved dosage when it is absolutely necessary for the purpose of saving the patient's life with advance knowledge of the associated risk of such adverse health effects [Note 7)]
D. Cases in which the purpose/method of use is not confirmed to be proper (such as cases in which drugs are used in other ways than the indications approved by the Minister of Health, Labour and Welfare, or cases in which drugs have not been used in accordance with the PRECAUTIONS of the electronic package inserts)
E. Cases of adverse health effects caused by drugs, etc. not considered eligible for the Relief System
   Drugs, etc. not considered eligible include [Note 8)]:
   i Drugs used for the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
   ii Drugs that do not have the possibility to cause ADRs, including drugs not to be used directly on human bodies or drugs without pharmacological effects (insecticides, disinfectant agents, in vitro diagnostics, etc.)
F. Cases of mild adverse health effects (Treatment equivalent to inpatient care associated with hospital admission is not required.) or cases in which disabilities caused by drugs fail to meet the disability criteria under the Relief System [Note 9)]
G. Cases in which 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 in which disorders or disabilities are considered unlikely to have been caused by ADRs (those that are not considered to be due to drugs, etc.)
   • Cases in which it cannot be judged whether there is a causal relationship or whether drugs are used for the proper use and with the proper method because of insufficient documentation (impossible to judge)

## 7.Closing remark

Healthcare professionals are encouraged to fully check the necessary precautions in the electronic package inserts before using drugs, etc. and to use them properly. Please note that cases in which drugs, etc. are not used properly may not be eligible to receive relief benefits under the Relief System, even if the adverse health effects are suspected to have been caused by ADRs related to the drugs, etc. In addition, off-label uses are not covered by the Relief System, unless the intended use is widely practiced in clinical settings based on certain evidence, such as guidelines that specify such use.

Also, an input field for information on the Relief System has been newly added since June 2014 to the form of the Pharmaceuticals and Medical Devices Safety Information Report, the form for healthcare professionals to report adverse drug reactions. The input field lists options such as “the patient intends to claim” and “the Relief System was introduced to the patient” as choices to describe the situation related to the Relief System. Healthcare professionals who are reporting adverse reactions to drugs are requested to consider introducing the Relief System to the patient.

If ADRs, etc. occur or healthcare professionals are consulted by their patients about ADRs, they should provide information on the Relief System to the patients or their caregivers when the adverse health effects are possibly applicable to receiving relief benefits under the Relief System. The 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 claims and cases of payment/non-payment.
https://www.pmda.go.jp/kenkouhigai_camp/ (only in Japanese)

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

• Relief System Consultation Service, the 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) From: FY 2023 Awareness Survey on the Relief System for Adverse Drug Reaction
https://www.pmda.go.jp/relief-services/adr-sufferers/0023.html (only in Japanese)
and from: FY 2024 Relief Service Committee (the PMDA)
https://www.pmda.go.jp/about-pmda/advisory-council-information/relief-services/0059.html (only in Japanese)

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

Note 3) The number of cases is on an applicant basis. If there is a second claim for the same cause after the first claim, the 2 applications are counted as 1 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/000153788.pdf (in English)

Note 5) Serious Skin Disorders with Lamotrigine and Adherence to Dosage and Administration
https://www.pmda.go.jp/files/000231989.pdf (in English)

Note 6) “The persons liable for the damages” refers to, typically, the persons responsible for accidents caused by adulterated drugs or contaminated drugs, so-called defective drugs.

Note 7) Cases where the sufferer’s tolerance of the ADR that occurred can be reasonably expected.
Typical situations in which such tolerance is expected are as follows:

(1) The drug is used in critical care situations.
(2) There are no alternative treatment modalities available.
(3) A higher dose of the drug than the usual 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 had been recognized in advance mentioned in (4) occurred.

Whether an individual case requires tolerance by sufferers will be judged based on these typical situations, and it must have the same degree of validity for tolerance as these situations in terms of what can be reasonably expected. 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. not eligible for relief benefits
https://www.pmda.go.jp/relief-services/adr-sufferers/0044.html (only in Japanese)

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 the patient’s daily life activities (Grade 2)”

# Efforts for Relief Regarding Human Papillomavirus Vaccine Under the Relief System

## 1. Introduction

The joint meeting of the Adverse Reactions 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 papilloma virus vaccine (hereinafter referred to as “HPV vaccines”) was held on September 17, 2015. Based on the deliberations of the joint meeting, under the Relief System, the MHLW/PMDA has promptly reviewed the relief claims for claimants who claim adverse health effects for symptoms that occurred after administration of HPV vaccines and has taken efforts to increase awareness of the Relief System. By the end of March 2024, for 321 patients out of the 540 patients reviewed, it had been acknowledged that a causal relationship between HPV vaccines and health effects was reasonably possible.

People who were vaccinated under the “Urgent Vaccination Promotion Such as for Cervical Cancer Vaccines” Note) from November 26, 2010 to March 31, 2013 may be eligible to receive support for medical expense/medical allowance payments from the Public Foundation of the Vaccination Research Center, even in cases where the medical care required was not of an extent to be considered to be equivalent to inpatient care, including cases where patients received treatment on an outpatient basis, if the adverse health effects are considered to be possibly related to vaccination as a result of the review for the relief benefits.

If support for medical expenses/medical allowances is to be provided for the first time for any adverse health effect caused by the vaccination in this program, a claim for relief benefits must first be submitted for the Relief System regardless of the level of medical care such as inpatient or outpatient care. Therefore, healthcare professionals are requested to cooperate with the claimant’s procedures (creation of medical certificates, etc.).

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

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

## 2. Results of health damage relief under the Relief System

The results (annual trends) of health damage relief under the Relief System for adverse drug reactions to HPV vaccines have been reported as shown in the following table.Note)

| Fiscal year | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|---|
| Number of claims | 2 cases | 10 cases | 7 cases | 25 cases | 39 cases | 152 cases |
| Number of payments | No cases | 5 cases | 9 cases | 8 cases | 4 cases | 75 cases |
| Fiscal year | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
| Number of claims | 334 cases | 141 cases | 86 cases | 59 cases | 34 cases | 20 cases |
| Number of payments | 314 cases | 223 cases | 111 cases | 75 cases | 49 cases | 29 cases |
| Fiscal year | 2022 | 2023 | Total | | | |
| Number of claims | 9 cases | 6 cases | 924 | | | |
| Number of payments | 8 cases | 13 cases | 923 | | | |

(Source: PMDA Annual Report FY 2023)
https://www.pmda.go.jp/about-pmda/annual-reports/0001.html (only in Japanese)

Note) More than one type of benefit may be claimed in a single claim. Also, a single claimant may

submit multiple claims successively for a single claim.

## 3. Points to be considered in regard to the necessary documentation when claiming relief benefits under the Relief System in relation to HPV vaccines, etc.

The MHLW issued an administrative notice in 2016 concerning items to be considered in regard to the necessary documentation when claiming relief benefits. Please read through the details of the administrative notice shown below.

1. Medical certificate
   (1) Medical certificates are only required for medical care related to the adverse health effect for which claims are being filed, regardless of whether the care is provided on an inpatient or outpatient basis. Claimants do not need to request all medical institutions they visited to create medical certificates.
   (2) For the medical certificates, please cooperate by providing information necessary to judge the causal relationship to the vaccination, such as information regarding the day of vaccination and the clinical course until the onset of symptoms, which is considered to be important, as far as reasonably possible. It is also permissible to include information other than the treatment by the medical institution that created the medical certificate (for example, information related to the duration of treatment in cases where the patient consulted with multiple medical institutions because of ambiguous symptoms, as well as information on the symptoms that triggered hospital consultation).
   Claimants are also encouraged to attach materials related to other medical institutions (addresses, telephone numbers, date 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 by the medical institution or if the materials have only partial information.
2. 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 screening questionnaires provided prior to vaccination or other reference materials (such as body temperature results, items asked about during the medical interview or examination), and attach them to the claim document .

**From the administrative notice issued on January 14, 2016 by the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, "Items to Be Considered in Regard to the 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-General of the Health Service Bureau, MHLW and the Director-General of the Sports and Youth Bureau, MEXT, dated September 30, 2015, "Enhancement of Consultation and Support Systems for Sufferers of Symptoms after Human Papillomavirus Infection Vaccination" (HSB Notification No. 0930-7, 27 SYB Notification No. 419)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/madoguchi/dl/151116_02.pdf (only in Japanese)
•Administrative Notice by the Health Service Division, Health Service Bureau and the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated October 22, 2015, "Increasing Awareness of Deadlines for the Relief System for Adverse Drug Reactions Claims in Relation to Vaccination Under "Urgent Vaccination Promotion Such as for Cervical Cancer vaccines (Request)"
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/dl/yobou151022-1.pdf (only in Japanese)

•Administrative Notice by the Health Service Division, Health Service Bureau, MHLW, dated December 1, 2015, “Relief Benefits for Adverse Health Effects Due to “Urgent Vaccination Promotion Such as for Cervical Cancer Vaccines” (Request)”
https://www.pmda.go.jp/files/000208632.pdf (only in Japanese)
•Administrative notice by the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated January 14, 2016, “Items to Be Considered in Regard to Necessary Documentation When Claiming Relief Benefits Under the Relief System for Adverse Drug Reaction in Relation to Vaccination Under “Urgent Vaccination Promotion Such as for Cervical Cancer Vaccines””
https://www.pmda.go.jp/files/000209731.pdf (only in Japanese)
•Notification by the Director of the Office of Drug Induced Damages, General Affairs Division and the Director of the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated January 15, 2016, “Request for Cooperation for the Relief System for Adverse Health Effects Provided by the PMDA” (PSEHB/GAD/ODID Notification No. 0115-1 and PSEHB/SD Notification No. 0115-1)
https://www.pmda.go.jp/files/000209915.pdf (only in Japanese)
•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

# Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated November 13, 2024, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

## 1 Triamcinolone acetonide (ophthalmic injection)

| | |
|---|---|
| **Brand name (name of company)** | MaQaid Ophthalmic Injection 40 mg (Wakamoto Pharmaceutical Co., Ltd.) |
| **Therapeutic category** | Agents for ophthalmic use |
| **Indications** | <Intravitreal injection><br>·Visualization of the vitreous body during vitreous surgery<br>·Diabetic macular oedema<br><Subtenon injection><br>Alleviation of macular oedema associated with the following diseases<br>·Diabetic macular oedema<br>·Retinal vein occlusion<br>·Noninfective uveitis |

**PRECAUTIONS (Revised language is underlined.)**

| | |
|---|---|
| **8.IMPORTANT PRECAUTIONS (newly added)** | <Subtenon injection><br><u>Infective scleritis may occur. Patients should be closely monitored after administration of this drug. The patients must be instructed to immediately consult physicians if any abnormalities are observed.</u> |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | <u><Intravitreal injection: Visualization of the vitreous body during vitreous surgery></u><br><u>Eye disorders</u><br><u>Endophthalmitis may occur. Surgical intervention may be needed.</u><br><Subtenon injection><br>Eye disorders<br>Cataract, increased intraocular pressure, glaucoma<u>, or infective scleritis</u> may occur. Surgical intervention may be needed. |
| **Reference information** | Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports<br>Cases involving endophthalmitis reported in Japan for <Intravitreal injection: Visualization of the vitreous body during vitreous surgery>: 3 (including 1 case in which this drug was not completely removed from the patient who did not comply with PRECAUTIONS) (No patient mortalities)<br><br>Cases involving infective scleritis reported in Japan for <Subtenon injection>: 5 (including 2 cases in which the drug was administered outside the approved indications) (No patient mortalities) |

Number of patients using the drug as estimated by the MAH during the previous 1-year period:
<Intravitreal injection> Visualization of the vitreous body during vitreous surgery
Approximately 87,000
<Intravitreal injection> Diabetic macular oedema
Approximately 16,000
<Subtenon injection> Alleviation of macular oedema associated with diabetic macular oedema/retinal vein occlusion/noninfective uveitis
Approximately 40,000

Japanese market launch: December 2010

## Case summary

| No. | Patient | | Daily dose/ Administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Female 80s | Macular oedema associated with branch retinal vein occlusion (hypertension, dementia) | Unknown for 1 day | **Nocardia scleritis and its aggravation [left eye]** | |
| | | | | Day of administration | Triamcinolone acetonide was administered by subtenon injection for macular oedema due to branch retinal vein occlusion of the left eye. |
| | | | | 49 days after administration (day of onset) | Scleritis occurred. Administration of antibiotic eye drops and betamethasone sodium phosphate eye drops was initiated. |
| | | | | 63 days after administration | The symptoms were aggravated. Inflammatory cells in the anterior chamber occurred. Frequent administration of levofloxacin hydrate eye drops and cefmenoxime eye drops and oral administration of levofloxacin hydrate were additionally initiated. |
| | | | | 70 days after administration | Eye pain/conjunctival hyperaemia of the left eyes, nodular lesions accompanied by pleural necrosis, inflammatory cells in the anterior chamber, and fibrin precipitation occurred. Oral administration of prednisolone and cefdinir was initiated. |
| | | | | 86 days after administration | Hyperaemia improved and nodular lesions shrunk. Oral administration of cefdinir was completed. Fluorometholone eye drops were additionally initiated, and oral administration of prednisolone was gradually tapered. |
| | | | | 100 days after administration | Temporal scleral thinning and uvea were visualized. Only levofloxacin hydrate eye drops were used as antibiotics. |
| | | | | 142 days after administration | Redness and swelling around the left eye occurred. The dose of oral administration of prednisolone was increased, and eye drops were changed from fluorometholone to betamethasone sodium phosphate. Administration of moxifloxacin hydrochloride eye drops was initiated, and administration of cefdinir was resumed. |
| | | | | 146 days after administration | Swelling, redness, painful eye movement, and hyperaemia in the left eye were aggravated. Temporal orbital abscess in the left eye occurred. |
| | | | | 149 days after administration | The patient was admitted to the hospital. Drip infusion of cefazolin sodium hydrate was initiated. |
| | | | | 150 days after administration | Nodular lesions were disintegrated, and drainage was performed. The left eye swelling and conjunctival hyperaemia tended to improve. Moxifloxacin hydrochloride eye drops were switched to levofloxacin hydrate eye drops, and oral administration of prednisolone was tapered. Betamethasone sodium phosphate eye drops were switched to betamethasone sodium phosphate/fradiomycin sulfate eye drops. |
| | | | | 155 days after administration | Orbital abscess shrunk. *Nocardia elegans* was detected. Oral administration of sulfamethoxazole/trimethoprim was initiated. |
| | | | | 167 days after administration | The patient was discharged from the hospital. |
| | | | | 190 days after administration | Orbital abscess shrunk to a trace level. |

**Laboratory test value**

| Test item | 70 days after administration | 190 days after administration |
|---|---|---|
| Visual acuity right (corrected visual acuity) | 0.1 (1.0) | (0.9) |
| Visual acuity left (corrected visual acuity) | 0.03 (0.06) | (0.2) |

Concomitant drugs: Unknown

## Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/<br>Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/<br>age</th><th>Reason for use<br>(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td rowspan="12">2</td><td rowspan="12">Male<br>60s</td><td rowspan="12">Macular oedema associated with branch retinal vein occlusion<br>(blurred vision, conjunctival oedema, increased intraocular pressure)</td><td rowspan="12">20 mg<br>for 1 day</td><td colspan="2">Fungal scleritis</td></tr>
<tr><td>Day of administration</td><td>Triamcinolone acetonide was administered by subtenon injection on the lower nasal side of the left eye for macular oedema due to branch retinal vein occlusion.</td></tr>
<tr><td>40 days after administration</td><td>Increased intraocular pressure was observed, and administration of dorzolamide eye drops was initiated.</td></tr>
<tr><td>78 days after administration</td><td>Pain and hyperaemia in the left eye occurred. Administration of dorzolamide eye drops was discontinued.</td></tr>
<tr><td>84 days after administration<br>(day of onset)</td><td>Hyperaemia and pain did not improve, and conjunctival oedema occurred.</td></tr>
<tr><td>90 days after administration</td><td>Anterior chamber inflammation cells, posterior synechiae of iris, inferonasal subconjunctival yellow lesions, and lesions suggestive of abscess within posterior Tenon were confirmed. Subconjunctival injection of dibekacin sulfate and oral administration of cefpodoxime proxetil were initiated. However, the symptoms did not improve.</td></tr>
<tr><td>Date unknown</td><td>Miconazole eye drops, oral administration of voriconazole, and ophthalmic ointments of pimaricin were initiated.</td></tr>
<tr><td>Date unknown</td><td>Scedosporium was detected from the specimens of subconjunctival yellow lesions.</td></tr>
<tr><td>101 days after administration</td><td>Extensive serous retinal detachment was confirmed, and the range of abscess was extended.</td></tr>
<tr><td>102 days after administration</td><td>Although surgical debridement was performed, it was difficult to dissect the abscess.</td></tr>
<tr><td>109 days after administration</td><td>Intravenous infusion of fluconazole and subtenon injection of miconazole were initiated. Miconazole was administered by subtenon injection 9 times in total at a frequency of twice a week. Subocular margin abscess and ocular inflammatory changes shrunk. Subtenon abscess in anterior segment and scleral hyperaemia tended to improve gradually.</td></tr>
<tr><td>300 days after administration</td><td>The site of abscess became scarred, and serous retinal detachment disappeared.</td></tr>
<tr><td colspan="6">Laboratory test value
<table>
<tr><th></th><th>Day of administration</th><th>40 days after administration</th><th>84 days after administration</th><th>300 days after administration</th><th>496 days after administration</th></tr>
<tr><td>Visual acuity left (corrected visual acuity)</td><td>(1.0)</td><td>(0.9)</td><td>(0.2)</td><td>Counting finger at 10 cm</td><td>Hand motion</td></tr>
</table></td></tr>
<tr><td colspan="6">Concomitant drugs: Chlorhexidine gluconate, iodine/partially hydrolyzed polyvinyl alcohol, gatifloxacin hydrate eye drops, ofloxacin ophthalmic ointments</td></tr>
</table>

# 3

# Revisions of PRECAUTIONS (No. 355)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated November 13, 2024.

## 1 Psychotropic agents
## Lithium carbonate

| | |
|---|---|
| **Brand name** | Limas tablets 100, 200 (Taisho Pharmaceutical Co., Ltd.), and the others |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(newly added)** | Drug-induced hypersensitivity syndrome<br>Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, hepatic impairment, etc. that may occur even after discontinuation of administration. |

## 2 Agents for ophthalmic use
## Triamcinolone acetonide (ophthalmic injection)

| | |
|---|---|
| **Brand name** | MaQaid Ophthalmic Injection 40 mg (Wakamoto Pharmaceutical Co., Ltd.) |
| **8. IMPORTANT PRECAUTIONS**<br>**(newly added)** | <Subtenon injection><br>Infective scleritis may occur. Patients should be closely monitored after administration of this drug. The patients must be instructed to immediately consult physicians if any abnormalities are observed. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(newly added)** | <Intravitreal injection: Visualization of the vitreous body during vitreous surgery><br>Eye disorders<br>Endophthalmitis may occur. Surgical intervention may be needed.<br><Subtenon injection><br>Eye disorders<br>Cataract, increased intraocular pressure, glaucoma, or infective scleritis may occur. Surgical intervention may be needed. |

## 3 Other agents affecting nervous system and sensory organs
## Aceneuramic acid

| | |
|---|---|
| **Brand name** | Acenobel Extended Release Tablets 500 mg (Nobelpharma Co., Ltd.) |
| **8. IMPORTANT PRECAUTIONS** | (deleted) |
| **15. OTHER PRECAUTIONS**<br>**15.2 Information Based on Nonclinical Studies** | (deleted) |

4 Agents for hyperlipidemias, other agents relating to blood and body fluids,

## Ethyl icosapentate (300 mg, 600 mg, 900 mg)

| | |
|---|---|
| **Brand name** | Epadel Capsules 300, Epadel S Capsules 300, 600, 900 (Mochida Pharmaceutical Co., Ltd.), and the others |
| **11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)** | Atrial fibrillation, atrial flutter<br>It was reported that an increased risk of atrial fibrillation or atrial flutter requiring hospitalization was observed in the overseas clinical trial of ethyl icosapentate (4g/dayNote)). In addition, it was reported that an increased risk of atrial fibrillation was observed in Japanese and overseas clinical studies of omega-3-acid ethyl esters including those of ethyl icosapentate.<br>Note) The approved maximum daily dose of ethyl icosapentate is 2,700 mg for hyperlipidaemia. |

5 Agents for hyperlipidemias

## Ethyl icosapentate (2 g)

| | |
|---|---|
| **Brand name** | Epadel EM Capsules 2 g (Mochida Pharmaceutical Co., Ltd.) |
| **11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)** | Atrial fibrillation, atrial flutter<br>It was reported that an increased risk of atrial fibrillation or atrial flutter requiring hospitalization was observed in the overseas clinical trial of ethyl icosapentate (4g/day). In addition, it was reported that an increased risk of atrial fibrillation was observed in Japanese and overseas clinical studies of omega-3-acid ethyl esters including those of ethyl icosapentate. |

6 Agents for hyperlipidemias

## Omega-3-acid ethyl esters

| | |
|---|---|
| **Brand name** | Lotriga Granular Capsules 2 g (Takeda Pharmaceutical Company Limited) and the others |
| **11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)** | Atrial fibrillation, atrial flutter<br>It was reported that an increased risk of atrial fibrillation or atrial flutter requiring hospitalization was observed in the overseas clinical trial of ethyl icosapentate (4g/day). In addition, it was reported that an increased risk of atrial fibrillation was observed in Japanese and overseas clinical studies of omega-3-acid ethyl esters including those of ethyl icosapentate. |

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

## Hydroxychloroquine sulfate

| | |
|---|---|
| **Brand name** | Plaquenil Tablets 200 mg (Sanofi K.K.), and the others |
| **8. IMPORTANT PRECAUTIONS (newly added)** | Symptoms related to phospholipid accumulation may occur in organs/tissues such as the heart, kidney, muscle, and nervous system. Patients should be carefully monitored. Discontinuation of administration should be considered if any adverse reactions related to phospholipid accumulation are suspected. |

8 Antibiotic preparations acting mainly on mold

## Voriconazole

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

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS** | Serious blood disorder, serious renal disorder, and hyperkalaemia may occur. Patients should be carefully monitored through methods including periodic blood tests, renal function tests, and blood electrolyte tests prior to administration of this drug. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | Hyperkalaemia |

9 Drugs for improving serum high cholesterol

## Ethyl icosapentate (OTC drug)

**Brand name**

Epadel T (Mochida Pharmaceutical Co., Ltd.)

**Consultation (newly added)**

If the following symptoms are observed after taking this drug, they may be adverse reactions. In such cases, the use of this drug should be immediately discontinued, and a physician or pharmacist should be consulted, presenting them with this document.

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

| Name of symptoms | Symptoms |
|---|---|
| Atrial fibrillation, atrial flutter | Symptoms such as palpitations, chest discomfort, dizziness, skipped heartbeats may occur. |

# 4

# List of Products Subject to Early Post-marketing Phase Vigilance

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

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

| | Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiation |
|---|---|---|---|
| ◎ | Tapinarof<br>Vtama cream 1% | Japan Tobacco Inc. | October 29, 2024 |
| ◎ | Gumarontinib hydrate<br>Haiyitan tablets 50 mg | Haihe Biopharma K.K. | October 11, 2024 |
| ◎ | Live attenuated influenza vaccine<br>Flumist Intranasal Spray | Daiichi Sankyo Co., Ltd. | October 3, 2024 |
| | Coronavirus (SARS-CoV-2) RNA Vaccine[*1]<br>Kostaive intramuscular injection | Meiji Seika Pharma Co., Ltd. | September 30, 2024 |
| | Brexpiprazole[*2]<br>Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg | Otsuka Pharmaceutical Co., Ltd. | September 24, 2024 |
| | Treprostinil[*3]<br>Treprost Inhalation Solution 1.74 mg | Mochida Pharmaceutical Co., Ltd. | September 24, 2024 |
| | Inactivated tissue culture tick-borne encephalitis vaccine<br>Ticovac suspension liquid for intramuscular injection 0.5 mL, Ticovac Junior suspension liquid for intramuscular injection 0.25 mL | Pfizer Japan Inc. | September 13, 2024 |
| | Freeze-dried human protein C concentrate<br>Ceprotin for Intravenous Injection 1000 IU | Takeda Pharmaceutical Company Limited | September 6, 2024 |
| | Pneumococcal 20-valent conjugate vaccine adsorbed (mutated diphtheria $CRM_{197}$ conjugate)[*4]<br>Prevenar 20 Suspension Liquid for Injection | Pfizer Japan Inc. | August 30, 2024 |
| | Brivaracetam<br>Briviact Tablets 25 mg, 50 mg, Briviact for I.V. injection 25 mg | UCB Japan Co. Ltd. | August 30, 2024 |

This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

| Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiation |
|---|---|---|
| Mepolizumab (genetical recombination)[*5]<br>Nucala solution for s.c. injection 100 mg | GlaxoSmithKline K.K. | August 28, 2024 |
| Maribavir<br>Livtencity tablets 200 mg | Takeda Pharmaceutical Company Limited | August 28, 2024 |
| Vilanterol trifenatate/fluticasone furoate<br>Relvar 50 Ellipta 14 doses for Pediatric, Relvar 50 Ellipta 30 doses for Pediatric | GlaxoSmithKline K.K. | August 23, 2024 |
| Pirtobrutinib<br>Jaypirca Tablets 50 mg, 100 mg | Eli Lilly Japan K.K. | August 21, 2024 |
| Zinc histidine hydrate<br>Zintus Tablets 50 mg | Nobelpharma Co., Ltd. | August 20, 2024 |
| Momelotinib hydrochloride hydrate<br>Omjjara Tablets 100 mg, 150 mg, 200 mg | GlaxoSmithKline K.K. | August 15, 2024 |
| Iptacopan hydrochloride hydrate<br>Fabhalta capsules 200 mg | Novartis Pharma K.K. | August 15, 2024 |
| Favipiravir[*6]<br>Avigan Tablets 200 mg | FUJIFILM Toyama Chemical Co., Ltd. | August 15, 2024 |
| Sargramostim (genetical recombination)<br>Sargmalin for inhalation 250 μg | Nobelpharma Co., Ltd. | July 29, 2024 |
| Fluciclovine ($^{18}$F) Injection<br>Axumin Injection | Nihon Medi-Physics Co., Ltd. | July 2, 2024 |
| Concizumab (genetical recombination)[*7]<br>Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg | Novo Nordisk Pharma Ltd. | June 24, 2024 |
| Vilanterol trifenatate/fluticasone furoate<br>Relvar 100 Ellipta 14 doses, 30 doses | GlaxoSmithKline K.K. | June 24, 2024 |
| Zolbetuximab (genetical recombination)<br>Vyloy for I.V. infusion 100 mg | Astellas Pharma Inc. | June 12, 2024 |
| Nemolizumab (genetical recombination)[*8]<br>Mitchga Vials 30 mg | Maruho Co., Ltd. | June 11, 2024 |
| Susoctocog alfa (genetical recombination)<br>Obizur Intravenous Injection 500 | Takeda Pharmaceutical Company Limited | June 10, 2024 |
| Recombinant respiratory syncytial virus vaccine[*9]<br>Abrysvo intramuscular injection | Pfizer Japan Inc. | May 31, 2024 |
| Lebrikizumab (genetical recombination)<br>Ebglyss Subcutaneous Injection Syringes 250 mg, Ebglyss Subcutaneous Injection Autoinjectors 250 mg | Eli Lilly Japan K.K. | May 31, 2024 |
| Apadamtase alfa (genetical recombination)/ cinaxadamtase alfa (genetical recombination)<br>Adzynma Intravenous 1500 | Takeda Pharmaceutical Company Limited | May 30, 2024 |
| Cysteamine hydrochloride<br>Cystadrops Ophthalmic Solution 0.38% | Viatris Pharmaceuticals Japan Inc. | May 30, 2024 |

| Nonproprietary name<br>Brand name | | Name of the MAH | Date of EPPV initiation |
|---|---|---|---|
| | Lonafarnib<br>Zokinvy capsules 50 mg, 75 mg | AnGes, Inc. | May 27, 2024 |
| | Elranatamab (genetical recombination)<br>Elrexfio S.C. Injection 44 mg, 76 mg | Pfizer Japan Inc. | May 22, 2024 |
| | Capivasertib<br>Truqap tablets 160 mg, 200 mg | AstraZeneca K.K. | May 22, 2024 |
| | Nirsevimab (genetical recombination)<br>Beyfortus 50 mg solution for intramuscular injection in syringe, Beyfortus 100 mg solution for intramuscular injection in syringe | AstraZeneca K.K. | May 22, 2024 |
| | Belumosudil mesilate<br>Rezurock Tablets 200 mg | Meiji Seika Pharma Co., Ltd. | May 22, 2024 |
| | Crovalimab (genetical recombination)<br>Piasky for Injection 340 mg | Chugai Pharmaceutical Co., Ltd. | May 22, 2024 |
| | Sacubitril valsartan sodium hydrate*10<br>Entresto Granules for Pediatric 12.5 mg, 31.25 mg | Novartis Pharma K.K. | May 22, 2024 |
| | Luspatercept (genetical recombination)<br>Reblozyl for S.C. injection 25 mg, 75 mg | Bristol-Myers Squibb K.K. | May 20, 2024 |
| | Letermovir*11<br>Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg | MSD K.K. | May 17, 2024 |

*1 Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

*2 Excessive motor activity or physically/verbally aggressive behavior due to rapid changes in mood, irritability, and/or outbursts associated with dementia due to Alzheimer's disease

*3 Pulmonary hypertension associated with interstitial lung disease

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

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

*6 Severe fever with thrombocytopenia syndrome virus infection

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

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

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

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

*11 Prophylaxis of cytomegalovirus infections in organ transplant recipients