# Pharmaceuticals and Medical Devices Safety Information

## No. 405 November 2023

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

Available information is listed here

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

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

Register here


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

# Pharmaceuticals and Medical Devices Safety Information

**No. 405 November 2023**

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 only available in Japanese.)

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

## Abbreviations

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| CMV | Cytomegalovirus |
| DIHS | Drug-induced Hypersensitivity Syndrome |
| DRESS | Drug Reaction With Eosinophilia and Systemic Symptoms |
| EPPV | Early Post-marketing Phase Vigilance |
| FY | Fiscal Year |
| GAD | General Affairs Division |
| 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 |
| NSAIDs | Nonsteroidal Anti-inflammatory Drugs |
| ODID | Office of Drug Induced Damages |
| OTC | Over-the-Counter |
| PAB | Pharmaceutical Affairs Bureau |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PSD | Pharmaceutical Safety Division |
| PSEHB | Pharmaceutical Safety and Environmental Health Bureau |
| 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 resulting from routine vaccination and vaccinations such as COVID-19 vaccine, which is performed as a special temporary vaccination 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. However, adverse health effects resulting from voluntary vaccinations are eligible for relief under the Relief System or the Relief System for Infections Derived from Biological Products.

In the Relief System, a total of 29 014 cases have been granted relief benefits since its establishment in 1980 until the end of fiscal year (FY) 2022. 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.

## 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 (hereinafter referred to as "Drugs").

Drugs 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, 2023)]
Medical expenses (costs borne by the patients, not including health insurance payments)

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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)

• Actual costs of treatment for the disease caused by ADRs will be compensated.

Medical allowance (35 800 to 37 800 yen per month)

• Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs.

Disability pension (Grade 1: 2 875 200 yen per year, Grade 2: 2 299 200 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: 898 800 yen per year, Grade 2: 718 800 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 (2 514 000 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 family (7 542 000 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 (212 000 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 2022 was 36.1% in total according to the FY 2022 survey: 11.2% answered that they “were aware” of the Relief System and 24.9% 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 83.8% in total: 59.5% answered that they “were aware” of the Relief System and 24.3% answered that they “have heard about” the Relief System. By occupational category, awareness was 90.8% among physicians, 96.8% among pharmacists, 63.7% among nurses, and 85.2% 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 14.8% overall: 18.9% among physicians, 16.6% among pharmacists, 7.4% among nurses, and 13.5% among dentists. [Note 1)]

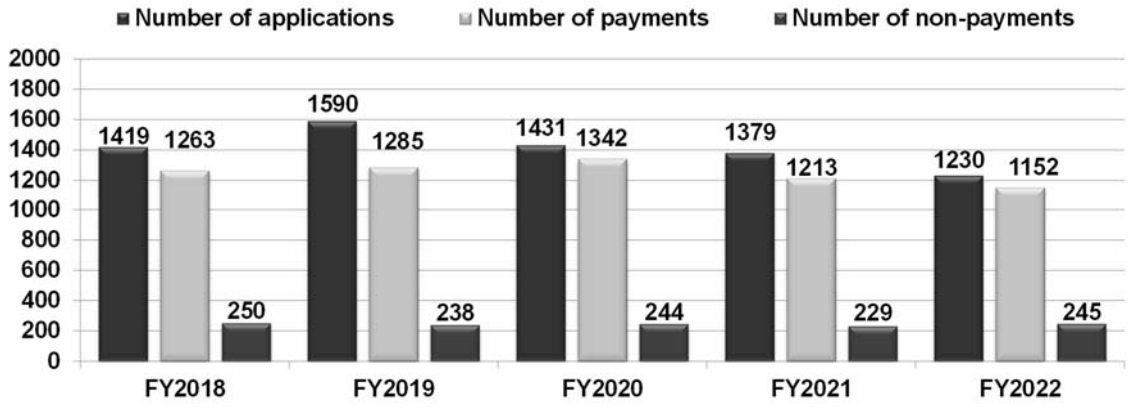
Furthermore, in all application forms related to relief benefits, the input field for “the source of information related to the Relief System” (selected from “Physician,” “Dentist,” “Pharmacist,” “Other medical facility staff,” “Newspaper/TV, etc.” and “Others”) was newly included in April 2016 to grasp the sources of information related to the Relief System. The FY 2022 results showed “Physician” in 378 answers (28.9%), “Others” (the Internet) in 242 answers (18.5%), “Pharmacist” in 138 answers (10.6%) 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 2018 and FY 2022 are shown in Figure 1. In FY2022, the number of applications was 1 230, the number of payments was 1 152, and the number of non-payments was 245. The ratios between payment and non-payment and details of reasons for non-payments from FY 2018 to FY 2022 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, and 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 2022 was 90.2%, which was the highest result greatly exceeding 60%.

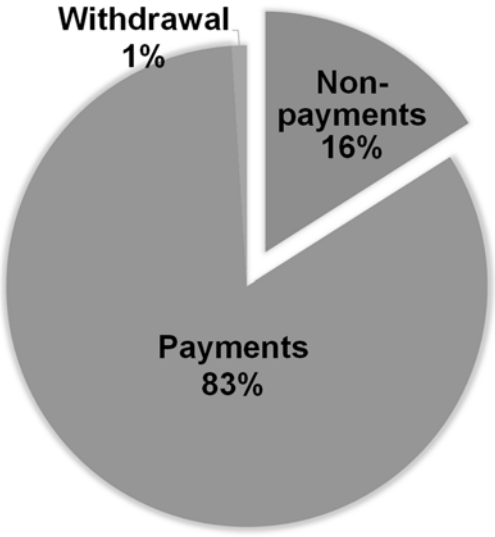
**Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2018 to FY 2022)**



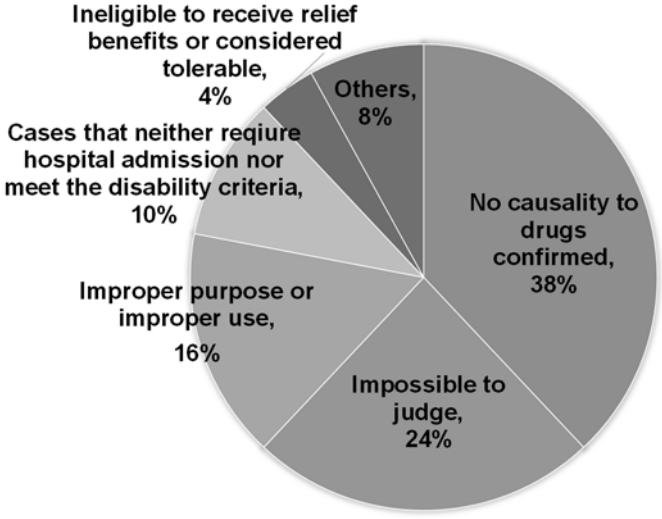

(Graph description)
*The number of cases is applicant-based. If there is a second claim for the same cause after the first claim, the 2 applications are counted as 1 case.
*Since it requires a certain period of time from the acceptance of a claim to the judgment to provide relief benefits, the number 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 2018 and FY 2022**

**Ratio of payments and non-payments**




**Breakdown of reasons for non-payments**



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

### 5.1 Cases of relief benefit payments

<Case 1> A case of anaphylaxis due to an influenza vaccine, for which medical expenses and medical allowance benefits were provided

A female in her 20s. She developed anaphylaxis following vaccination of Influenza HA Vaccine "Daiich Sankyo" Syringe 0.5 mL and received inpatient treatment. Medical expenses and medical allowance benefits were provided.

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

A male in his 60s. The patient developed anaphylactic shock after using Iomeron 350 Injection Syringe 135 mL (iomeprol). Subsequently, he died. Medical expenses, medical allowance benefits, bereaved family benefits, and funeral expenses benefits were provided.

<Case 3> A case of pulmonary thromboembolism due to eltrombopag olamine and higher brain dysfunction due to hypoxic encephalopathy secondary to pulmonary thromboembolism, which led to a disability status, for which medical expenses, medical allowance benefits, disability pension benefits were provided

A female in her 50s. She experienced pulmonary thromboembolism following the use of Revolade Tablets 12.5 mg (eltrombopag olamine) and received inpatient treatment. She had higher brain dysfunction due to hypoxic encephalopathy secondary to pulmonary thromboembolism. 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 40s. She experienced erythema multiforme type drug eruption following the use of Eve A Tablets 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, etc. was not considered proper)

Of the 1 206[Note 3)] non-payment cases from FY 2018 to FY 2022, the reason for nonpayment 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 of use of the drug, etc. was not considered proper (FY 2018 to FY 2022)**

| Name of causative drug | FY2018 | FY2019 | FY2020 | FY2021 | FY2022 | Total (cases) |
|---|---|---|---|---|---|---|
| Lamotrigine | 12 | 15 | 8 | 5 | 3 | 43 |
| Human chorionic gonadotrophin | 0 | 1 | 2 | 4 | 5 | 12 |
| Lithium carbonate | 1 | 3 | 0 | 3 | 4 | 11 |
| Thiamazole | 3 | 2 | 4 | 2 | 0 | 11 |
| Methotrexate | 1 | 4 | 5 | 1 | 0 | 11 |
| Others | 27 | 21 | 16 | 22 | 21 | 107 |
| Total (cases) | 44 | 46 | 35 | 37 | 33 | 195 |

**(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 disseminated papuloerythematous drug eruption due to lamotrigine (during titration period)**

A female in her 30s. She used Lamotrigine Tablets 25 mg "Towa" for bipolar disorder with drugs other than those inducing glucuronidation. Lamotrigine was started from a daily dose of 25 mg, which was increased to 50 mg/day after 11 days. The dose was further increased to 75 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 20s. She used Lamotrigine Tablets 25 mg "Sawai" for bipolar disorder with drugs other than those inducing glucuronidation. Lamotrigine was started from a daily dose of 50 mg as the first dose. Therefore, this drug use was not considered proper.

Improper use of lamotrigine

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 been continuously 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 dosages 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.

**Electronic package insert of Lamictal Tablets (revised in February 2022)**

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 | 100 mg/day | 50 mg/day | |

| | (once daily) | (twice daily in divided doses) | (once or twice in divided doses daily) |
|---|---|---|---|
| Week 5 | 50 mg/day (once or twice in divided doses daily) | 200 mg/day (twice daily in divided doses) | 100 mg/day (once or twice in divided doses daily) |
| After Week 6 | 100 mg/day (maximum 200 mg/day) (once or twice in divided doses daily) (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) (Dose should be increased by up to 100 mg/day 1 week or longer apart.) | 200 mg/day (maximum 400 mg/day) (once or twice in divided doses daily) (Dose should be increased by up to 100 mg/day 1 week or longer apart.) |

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 conducted, 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 Tablet 100 mg and 200 mg “Amel” 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 July 2021)** (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.

**<Case 2> A case of drug-induced liver injury due to benzbromarone**

Male in his 50s. Since no blood tests had been conducted for approximately 6 months until drug-induced liver injury was observed after the start of Benzbromarone Tablet 50 mg "NM" administration, the case was not approved as proper use.

**Description in the electronic package insert of Benzbromarone Tablet 500 mg "NM" (revised in April 2022)** (partial excerpt)

[Warnings]

Serious liver disorders such as fulminant hepatitis have been reported especially within the first 6 months after initiating administration, leading to serious outcomes such as death in some cases. Liver function tests should be periodically performed for at least the first 6 months after initiating administration. Patients should be carefully monitored, and if any abnormal liver function test results or jaundice are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

**(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 families or acquaintances, not for themselves, such uses will not be considered proper.

Healthcare professionals should provide definite instructions such as specific oral instructions in addition to the written instructions regarding dosing days, dosing conditions, and doses to allow patients to manage their drugs appropriately.

**<Case> A case of purpuric drug eruption due to famotidine OD**

A female in her 30s. As a result of taking Famotidine OD Tablets 10 mg "Ohara" for gastralgia, the occurrence of purpuric drug eruption was noted. Since the patient took the unused drugs that were previously prescribed 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 on treatment with Warfarin tablets (warfarin potassium), Florid Oral Gel (miconazole), whose co-administration is contraindicated, was used. Marked coagulopathy developed and was prolonged due to interactions, and purpura developed on 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 (revised in July 2019)** (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 also submit paper-based documents and 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 resulting from statutory vaccination practice (Relief System for Injury to Health with Vaccination is applicable under the Preventative Vaccination Law.) However, cases of adverse health effects resulting from 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 resulting from Drugs not considered eligible for the Relief System
   Drugs 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 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 and Food Sanitation 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 due to Drugs)
   • 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 alerts in the electronic package inserts before using Drugs and to use them properly. Please note that cases in which Drugs 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. 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, a 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 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.
https://www.pmda.go.jp/english/index.html

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, 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 2022 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 2023 Relief Service Committee (Pharmaceuticals and Medical Devices Agency) https://www.pmda.go.jp/about-pmda/advisory-council-information/relief-services/0056.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 and 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

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

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 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 2023, for 321 of the total 538 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 inpatient care, including cases where patients received treatment on an outpatient basis, and 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.).

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)

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

## 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 | 2016 |
|---|---|---|---|---|---|---|---|
| Number of claims | 2 cases | 10 cases | 7 cases | 25 cases | 39 cases | 152 cases | 334 cases |
| Number of payments | No cases | 5 cases | 9 cases | 8 cases | 4 cases | 75 cases | 314 cases |
| Fiscal year | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | Total |
| Number of claims | 141 cases | 86 cases | 59 cases | 34 cases | 20 cases | 9 cases | 918 cases |
| Number of payments | 223 cases | 111 cases | 75 cases | 49 cases | 29 cases | 8 cases | 910 cases |

(Source: PMDA Annual Report FY 2022)
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.

1. Medical certificate
   (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 all medical institutions they visited to create medical certificates.
   (2) For the medical certificates, 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, is considered important and should be provided as far as reasonably possible. It is also permissible for the medical institution creating the medical certificate to include other information than treatment (for example, information related to the duration of clinical practice if the patient consulted with multiple medical institutions since the symptoms were not apparent, symptoms that triggered hospital consultation, etc.).
   Please also cooperate with the attachment of materials related to other medical institutions (addresses, telephone numbers, days 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 for during the medical interview or examination), and attach them to the claims.

**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
# Revisions of PRECAUTIONS for Preparations Containing Acetaminophen (Prescription Drugs)

## 1. Introduction

Preparations containing acetaminophen (prescription drugs) are approved for marketing in Japan for the indication of mainly antipyretics and analgesics. Administration to 7 patient populations including “patients with peptic ulcer,” “patients with serious blood abnormalities,” “patients with serious liver disorder,” “patients with serious renal disorder,” “patients with serious cardiac function failure,” “patients with a history of hypersensitivity to any of the ingredients of acetaminophen preparations,” and “patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease” has been specified as a contraindication.

Recently, the language concerning contraindications, etc. for acetaminophen has been revised based on the deliberation in the 4th and 9th fiscal year (FY) 2023 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as “the Subcommittee on Drug Safety”) held on July 25 and September 21, 2023, respectively. This section will introduce the details of the revision.

Both the single active ingredient drugs of acetaminophen and the combination drugs containing acetaminophen including tramadol hydrochloride/acetaminophen combination drugs and diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/bromovalerylurea combination drugs (hereinafter referred to as “diprophylline/acetaminophen, etc. combination drugs”) were reviewed. However, the following combination drugs are not included in the drug products subject to this investigation for lifting the contraindications because they contain nonsteroidal anti-inflammatory drugs (hereinafter referred to as “NSAIDs”).

- Salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate combination drugs
- Salicylamide/acetaminophen/anhydrous caffeine/chlorpheniramine maleate combination drugs
- Isopropylantipyrine/acetaminophen/allylisopropylacetylurea/anhydrous caffeine combination drugs

## 2. Background

As shown in “1. Introduction,” administration of acetaminophen to the 7 patient populations has been specified as a contraindication. Japanese Association for the Study of Musculoskeletal Pain asked for lifting the contraindications for “patients with serious renal disorder” and “patients with serious cardiac function failure” among the patient populations on the basis of the reasons described below.

- Currently published standard textbooks, guidelines, etc. state that acetaminophen has less of an effect on renal function, fluid retention, etc. than NSAIDs, and that it can be a treatment option for patients in whom NSAIDs cannot be used.
- In actual clinical practice, cases are not rare in which acetaminophen is used in patients with renal disorder or cardiac function failure. However, specifying these patients as contraindications impedes appropriate drug therapy.

It was confirmed in related standard textbooks, guidelines, etc. that acetaminophen can be a treatment option for patients with peptic ulcer, blood abnormalities, or aspirin asthma in addition to these 2 patient populations. Therefore, it was decided to review the precautions for 5 patient

populations including “patients with serious renal disorder,” “patients with serious cardiac function failure,” “patients with peptic ulcer,” “patients with serious blood abnormalities,” and “patients with aspirin asthma (induction of asthmatic attack due to NSAIDs) or a history of the disease.”

Of note, as a result of re-evaluating indications and dosage and administration of the oral dosage forms of acetaminophen in 1994 (“Results of Re-evaluations of Drug Products in 1994 (No.2)” PAB Notification No.779 by the Director-General of Pharmaceutical Affairs Bureau (PAB), MHW dated September 8,1994), along with NSAIDs that were designated as drugs that should be re-evaluated simultaneously, these 5 populations were specified in the section of “This drug is contraindicated to the following patients” (currently CONTRAINDICATIONS). For the suppositories of acetaminophen, injections of acetaminophen, combination drugs, the contraindications were specified with reference to the oral dosage form.

## 3. Investigation results

Investigation results by the PMDA regarding the descriptions of the Japanese and overseas standard textbooks, guidelines, overseas product labeling, related published literature, etc. are as follows.

- “Patients with serious cardiac function failure,” “patients with peptic ulcer,” and “patients with serious blood abnormalities”

•The use of acetaminophen is recommended in standard textbooks, guidelines, published literature, etc.
•Contraindications for these patients are not listed in overseas product labeling.

- “Patients with serious renal disorder”

•The use of acetaminophen is recommended in standard textbooks, guidelines, published literature, etc.
•Although these patients are listed as contraindications in the Canadian product monograph for tramadol hydrochloride/acetaminophen combination drugs, it is due to tramadol hydrochloride. The product labeling of countries other than Canada does not list these patients as contraindicated.
•Adjustment of dosage and administration of acetaminophen is generally described in the overseas product labeling. However, consensus is not necessarily reached on the degree of renal disorder which requires adjusting dosage and administration of acetaminophen and the methods of adjusting them, since the language in overseas product labeling about adjustment of them is different and no clear descriptions are included in guidelines, etc.

- “Patients with aspirin asthma or a history of the disease”

•The use of acetaminophen is recommended in standard textbooks, guidelines, published literature, etc.
•Contraindications for these patients are not listed in overseas product labeling.
•Several Japanese guidelines state that 300 mg or less of acetaminophen per dose should be administered to the relevant patients.

Based on the above, the report stating the necessity of the following revisions for PRECAUTIONS of acetaminophen was prepared by the PMDA.

- Three patient populations including “patients with serious cardiac function failure,” “patients with peptic ulcer,” “patients with serious blood abnormalities” should be deleted from the CONTRAINDICATIONS section, and precautions should be provided in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS (in case of the new instructions; the Careful Administration in case of the old instructions; the same applies hereinafter) section.
- “Patients with serious renal disorder” should be deleted from the CONTRAINDICATIONS section. Also, a cautionary statement should be included in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section as follows: Adjustment of doses and dosing intervals of acetaminophen should be considered.
- “Patients with aspirin asthma (induction of asthmatic attack due to NSAIDs) or a history of the

disease" shall be as follows.

- For single active ingredient drugs and diprophylline/acetaminophen, etc. combination drugs, the description about patients with aspirin asthma should be deleted from the CONTRAINDICATIONS section, and a cautionary statement should be provided in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section. Also, in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION (in case of the new instructions; Precautions for Dosage and Administration in case of the old instructions; the same applies hereinafter) section for single active ingredient drugs, a cautionary statement should be provided as follows: 300 mg or less of acetaminophen per dose should be administered.
- For tramadol hydrochloride/acetaminophen combination drugs, which contain 325 mg of acetaminophen per tablet, "patients with aspirin asthma or a history of the disease" should be specified as contraindications as before for the indication of "pain after tooth extraction," for which the usual dose is 2 tablets per dose (650 mg of acetaminophen). For "non-cancerous chronic pain" for which the usual dose is 1 tablet per dose (325 mg of acetaminophen) and increasable to 2 tablets per dose (650 mg of acetaminophen), cautionary statements that "The dose should be 1 tablet per dose." and "Adjusting the dose using not the relevant combination drugs but single active ingredient preparations containing acetaminophen should be considered." should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section and the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section, respectively.

## 4. Deliberation, etc. by the Subcommittee on Drug Safety

Based on the investigation results and evaluation by the PMDA as described in "3. Investigation results," it was concluded that revision of PRECAUTIONS for acetaminophen was necessary.

For OTC drugs, considering the circumstances where patients can purchase OTC drugs without consulting a physician based on the information in the package insert, etc., it was decided not to change the description of the current package insert, since it is necessary to provide information more carefully. Healthcare professionals are advised to appropriately provide consultation to "patients who have developed asthma after using acetaminophen, other antipyretics and analgesics, and common cold medicines (patients with aspirin asthma or a history of the disease)," which are described in "When not to use the product" in the package insert, in line with the purpose of the revision of package insert for prescription drugs this time.

## 5. Closing remark

Healthcare professionals are requested to understand the purpose of the revision this time and to carefully check the electronic package insert to make a careful decision on the use of acetaminophen. Their continued cooperation for proper use of acetaminophen would be appreciated.

[References]


- Materials 1-1 to 1-4 of the 4th FY 2023 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on July 25, 2023)
  https://www.mhlw.go.jp/stf/newpage_34324.html (only in Japanese)
- Materials 2-1 to 2-2 of the 9th FY 2023 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on September 21, 2023)
  https://www.mhlw.go.jp/stf/newpage_35299.html (only in Japanese)
- Revision of PRECAUTIONS (PSEHB/PSD Notification No. 1012-2 dated October 12, 2023)
  https://www.pmda.go.jp/files/000264875.pdf (in Japanese)
  English translation by the PMDA (October 12, 2023)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0011.html

# 3

# Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated October 12, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

## 1 Apalutamide

| | |
|---|---|
| **Brand name (name of company)** | Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | •Castration-resistant prostate cancer without remote metastasis<br>•Metastatic prostate cancer |

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

**[Under new instructions]**

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS** | Severe skin disorders <u>and drug-induced hypersensitivity syndrome</u> may occur. If a rash occurs, a dermatologist should be consulted at an early stage, and temporary discontinuation or discontinuation of this drug should be considered. Patients should be instructed to immediately seek medical attention if any skin abnormalities are observed. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | <u>Drug-induced hypersensitivity syndrome</u><br><u>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.</u> |
| **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 drug-induced hypersensitivity reported in Japan: 2 (No patient mortalities)<br>Cases involving drug-induced hypersensitivity reported overseas: 2 (No patient mortalities)<br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 280<br>Japanese market launch: May 2019 |

## Case summary

| No. | Patient | | Daily dose/ administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Male 70s | Castration-resistant prostate cancer (none) | 240 mg for 140 days ↓ Discontinuation ↓ 120 mg approximately for 14 days ↓ Discontinuation | **Drug-induced hypersensitivity syndrome**<br>Medical history: Prostate cancer, lung cancer, chronic obstructive pulmonary disease, chronic renal disorder, obstructive arteriosclerosis of lower extremities, gout | |
| | | | | Day 1 of administration | Apalutamide was initiated (240 mg/day) for castration-resistant prostate cancer. |
| | | | | Day 140 of administration (day of discontinuation) | Red bean sized-oedematous erythema developed on the upper limbs and abdomen. Administration of apalutamide was discontinued. |
| | | | | Approximately 2 weeks after discontinuation (Day 1 of readministration) | Since skin eruption faded after suspension of apalutamide, the dose of apalutamide was reduced to 120 mg/day, and administration was resumed. |
| | | | | Approximately 2 weeks after readministration (day of discontinuation of readministration) | As skin eruption relapsed, administration of apalutamide was discontinued. Apalutamide was switched to enzalutamide 120 mg/day. |
| | | | | Date unknown | Administration of prednisolone 10 mg/day was initiated, but skin eruption did not improve. |
| | | | | 3 weeks to 1 month after discontinuation of readministration | The skin eruption was exacerbated and spread to the entire body. |
| | | | | Approximately 1 month after discontinuation of readministration | The patient visited the emergency outpatient department and was referred to the department of dermatology on the same day.<br>Generalized diffuse flushing with marked desquamation was noted. He had pyrexia of 38.6°C. No bulbar conjunctiva hyperaemia or oral erosion was noted. Palpation revealed no obvious swollen lymph nodes.<br>Blood pressure: 130/82 mmHg, heart rate: 111/min, $SpO_2$: 98%, consciousness: lucid.<br>White blood cell count: 11 100/μL (eosinophils: 4.3%, no atypical lymphocytes), AST: 26 U/L, ALT: 25 U/L, ALP: 218 U/L, LDH: 299 U/L, BUN: 23.8 mg/dL, Cre: 1.79 mg/dL (Cre before skin eruption: 1.49 mg/dL), CRP: 8.57 mg/dL. |
| | | | | 1 day after the initial consultation by the dermatologist (approximately 1 month after discontinuation of readministration) | Histopathological findings from the biopsy of the left upper arm skin: Hypertrophy of the epidermis, irregular prolongation of the epidermal ridges, and infiltration of inflammatory cells in the upper dermis were noted. Lymphocytes infiltrated in the epidermis, and epidermal intercellular oedema and individual cell necrosis of keratinocytes were observed. The majority of infiltrating lymphocytes were CD4 negative and CD8 positive. Erythroderma-type drug eruption due to apalutamide was diagnosed.<br>After the admission to the hospital, treatment with oral prednisolone 30 mg/day was initiated. After that, fever was brought down rapidly. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 10 days after the initial consultation by the dermatologist (approximately 40 days after discontinuation of readministration) | Since the skin eruption had a tendency to fade, the dose of prednisolone was reduced to 20 mg/day. |
| | | | | 12 days after the initial consultation by the dermatologist | There was no relapse, and the patient was discharged from the hospital. |
| | | | | 22 days after the initial consultation by the dermatologist (approximately 50 days after discontinuation of readministration) | Pyrexia and flushing relapsed. The patient was re-admitted to the hospital, and the dose of prednisolone was increased to 40 mg/day. |
| | | | | 23 days after the initial consultation by the dermatologist | Fever was brought down. |
| | | | | 27 days after the initial consultation by the dermatologist | Pyrexia developed again. The respiratory status was exacerbated. The department of respiratory medicine was consulted.<br>A chest CT revealed right-dominant bilateral ground-glass opacity in the lungs. Possible drug-induced interstitial pneumonia due to apalutamide was considered. |
| | | | | 28 days after the initial consultation by the dermatologist | Methylprednisolone 1 g/day (1 250 mg/day as prednisolone) was administered for 3 days. |
| | | | | 31 days after the initial consultation by the dermatologist (approximately 60 days after discontinuation of readministration) | The dose of prednisolone was reduced to 40 mg/day. |
| | | | | 32 days after the initial consultation by the dermatologist | Pyrexia and rapid exacerbation of the respiratory status were noted. Oxygenation was difficult to maintain even with oxygen administration at a high flow rate. β-D glucan increased. Complication of pneumocystis pneumonia was suspected. Administration of atovaquone was initiated. The skin eruption did not improve well. Diffuse flushing persisted. |
| | | | | 34 days after the initial consultation by the dermatologist | Cytomegalovirus (CMV) antigen was positive. Around the same time, HHV6-DNA, HHV7-TgG, and HIV 1/2 IgG were tested negative.<br>Specific virus reactivation was noted. Drug-induced hypersensitivity syndrome was diagnosed (drug reaction with eosinophilia and systemic symptoms (DRESS) score by RegiSCAR: 5 points). It was decided that the dose of prednisolone would be gradually reduced. |
| | | | | 38 days after the initial consultation by the dermatologist | The dose of prednisolone was reduced to 35 mg/day. Complication of CMV pneumonia was also suspected, and administration of valganciclovir was |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | initiated. After that, the respiratory status gradually improved. |
| | | | | 41 days after the initial consultation by the dermatologist (approximately 70 days after discontinuation of readministration) | EBV-DNA was positive. |
| | | | | 49 days after the initial consultation by the dermatologist | The respiratory status became steady. The normal skin area expanded. |
| | | | | 52 days after the initial consultation by the dermatologist (approximately 80 days after discontinuation of readministration) | The dose of prednisolone was reduced to 32.5 mg/day.<br>β-D glucan decreased. Negative conversion of CMV antigen was observed, and administration of atovaquone was terminated. |
| | | | | 58 days after the initial consultation by the dermatologist | Administration of valganciclovir was terminated. |
| | | | | 63 days after the initial consultation by the dermatologist (approximately 90 days after discontinuation of readministration) | Resting oxygen administration was required due to the organizing lung lesion. Since oxygenation markedly decreased on exertion, discharge from the hospital to home was considered difficult. The patient was transferred to another hospital. (The skin eruption had not resolved.) |
| | | | | Date unknown | The patient passed away at the hospital to which he was transferred. |
| | Suspected concomitant drugs: None<br>Concomitant drugs: Prednisolone, levocetirizine hydrochloride, mirabegron, ursodeoxycholic acid, rabeprazole sodium, L-carbocisteine, tiotropium bromide hydrate/olodaterol hydrochloride, sarpogrelate hydrochloride, allopurinol, magnesium oxide, sennoside | | | | |

| No. | Patient | | Daily dose/ administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 2 | Male<br>80s | Metastatic prostate cancer (none) | 240 mg<br>for 43 days<br>↓<br>Discontinuation | **Drug-induced hypersensitivity syndrome**<br>Medical history: Hypertension, dyslipidaemia, diabetes mellitus, prostate cancer, bladder cancer | |
| | | | | Date unknown | Administration of goserelin acetate (dose unknown) and silodosin (dose unknown) was initiated at least 1 year before the onset of skin eruption. |
| | | | | Day 1 of administration | Administration of apalutamide (240 mg/day) was initiated for metastatic castration-sensitive prostate cancer. |
| | | | | Day 38 of administration | Drug-induced hypersensitivity syndrome (DIHS) and pharyngodynia developed.<br>Erythema and skin eruption developed on the entire body.<br>Throat pain was present. Since COVID-19 infection was suspected, the patient visited the family doctor. SARS-CoV-2 was probably negative. Cefcapene pivoxil hydrochloride hydrate was prescribed and taken until Day 43. No contact to the attending physician was made, and no action was taken. |
| | | | | Day 43 of administration (day of discontinuation) | Malaise and vanishing bile duct syndrome developed. Pyrexia was also present. The patient had difficulty eating.<br>He visited the emergency outpatient department and was urgently admitted to the hospital. Administration of apalutamide was discontinued after confirming with the attending physician during the treatment in the outpatient department.<br>Cefcapene pivoxil hydrochloride hydrate (dose unknown) was discontinued.<br>Body temperature: 38.3°C. The entire face was red and swollen. Faint erythema was observed on the trunk and confluent erythema on the entire lower limbs (Erythema was noted over 90% of the body surface area). No enanthema was noted.<br>Swollen lymph nodes were palpable in the right and left neck, axilla, and groin. New erythema appeared at the site of pigmentation caused by the recovered erythema.<br>A skin biopsy (erythema on the right thigh) revealed liquefaction degeneration in the epidermal basal layer, inflammatory cell infiltration mainly consisting of lymphocytes, and individual cell necrosis in the epidermis. Infiltration of eosinophils, lymphocytes, and histiocytes was observed around the blood vessels in the superficial dermis.<br>Interface dermatitis was diagnosed.<br>A CT (cervical and thoracoabdominal simple) revealed enlarged lymph nodes in the neck, supraclavicular fossa, axilla, and mediastinum. Mild hepatosplenomegaly was noted.<br>Microbiological test: HBsAg (-), HBsAb (-), HBcAb (-), HCVAb (-).<br>TARC (Th2 chemokine) was markedly high at 29 700 pg/mL. |
| | | | | 1 day after discontinuation | Administration of prednisolone 70 mg/day (intravenous injection) was initiated. |
| | | | | Date unknown | The condition did not resolve even after the discontinuation of apalutamide. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Administration of goserelin acetate and silodosin was discontinued. |
| | | | | 6 days after discontinuation | Eosinophil count had a tendency to increase. The condition was very serious. |
| | | | | 7 days after discontinuation | Viral test was performed. HSV: Negative, EBV: Negative, HHV6-DNA: Negative<br>CMV activity was suspected (CMV IGG: 121, CMV IGM: 0.04, CMV antigenemia: Negative). |
| | | | | 8 days after discontinuation | The skin eruption was exacerbated. Erythema darker than 5 days after the onset was observed. Pyrexia also persisted. Eosinophil count increased to 49% (1 162/μL).<br>A skin biopsy (erythema on the back of the left hand) revealed liquefaction degeneration of the epidermal basal layer and inflammatory cell infiltration mainly consisting of lymphocytes severer than the first biopsy. Necrosis of individual cells increased as well.<br>Interface dermatitis was diagnosed. |
| | | | | 9 days after discontinuation | Administration of prednisolone 70 mg/day (oral) 3 times daily was initiated. |
| | | | | 11 days after discontinuation | Pulse administration of methylprednisolone sodium succinate 1 000 mg/day (intravenous injection) was initiated (until 13 days after discontinuation). DLST (apalutamide) was negative. |
| | | | | 12 days after discontinuation | The first plasma exchange therapy was performed. |
| | | | | 14 days after discontinuation | The second plasma exchange therapy was performed. Prednisolone 70 mg/day was administered (until 15 days after discontinuation). |
| | | | | 16 days after discontinuation | Prednisolone 60 mg/day was administered (until 21 days after discontinuation). |
| | | | | 19 days after discontinuation | The third plasma exchange therapy was performed. |
| | | | | 20 days after discontinuation | Body temperature was 38.9°C. After that, body temperature decreased. No pyrexia seemed to develop thereafter.<br>After a total of 3 sessions of plasma exchange therapy, skin eruption improved, fever declined, and eosinophil count decreased. |
| | | | | 21 days after discontinuation | Massive gamma globulin therapy was performed for 5 days. |
| | | | | 22 days after discontinuation | Prednisolone 50 mg/day was administered (until 31 days after discontinuation). |
| | | | | 26 days after discontinuation | High ALP level persisted. A liver biopsy showed severe infiltration of neutrophils and lymphocytes in the sinusoids and vanishing of the intrahepatic bile duct. Vanishing bile duct syndrome was diagnosed. |
| | | | | 28 days after discontinuation | Watery stools up to 10 times a day were observed after 28 days of discontinuation. |
| | | | | 29 days after discontinuation | HHV6-DNA was negative. |
| | | | | 31 days after discontinuation | CMV enterocolitis developed. |
| | | | | 32 days after discontinuation | Prednisolone 40 mg/day was administered (until 39 days after discontinuation). |
| | | | | Approximately 36 days after discontinuation | CMV antigenemia was positive. CMV enterocolitis was diagnosed. The patient was treated with ganciclovir and |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | valganciclovir. The symptoms of enterocolitis were remitted. |
| | | | | 40 days after discontinuation | Prednisolone 35 mg/day was administered (until 46 days after discontinuation). |
| | | | | 42 days after discontinuation | HHV6-DNA was negative. |
| | | | | Date unknown | Cutaneous symptoms were consistent with the characteristics of DIHS/DRESS, except that no HHV6 reactivation was observed during the clinical course. DIHS/DRESS was diagnosed (RegiSCAR score: 9 points). |
| | | | | 43 days after discontinuation | A colon biopsy was performed. CMV enterocolitis was diagnosed. |
| | | | | 46 days after discontinuation | CMV IGG was >250, and CMV IGM was 0.08. |
| | | | | 47 days after discontinuation | Prednisolone 30 mg/day was administered (until 59 days after discontinuation). |
| | | | | 48 days after discontinuation | CMV activity was suspected. HSV was negative. EBV was negative. |
| | | | | 55 days after discontinuation | DLST (apalutamide) was negative. |
| | | | | 60 days after discontinuation | Prednisolone (dose unknown, <30 mg/day) was administered (until 62 days after discontinuation). |
| | | | | 61 days after discontinuation | CMV enterocolitis was resolved. Vanishing bile duct syndrome was resolved. |
| | | | | 62 days after discontinuation | DIHS was resolved. The patient was discharged from the hospital to home. A patch test after completion of oral prednisolone was negative. |
| | | | | 77 days after discontinuation | After the discharge, no recurrence of skin eruption was noted. The bile duct enzyme levels returned to normal. The dose of prednisolone was reduced to 20 mg/day. |
| | | | | Date unknown | The dose of prednisolone was reduced by 5 mg every 2 weeks to 15 mg and by 2.5 mg every 2 weeks thereafter. Prednisolone was then discontinued approximately 6 months after the start of treatment.<br>After discontinuation of prednisolone, no relapse of skin eruption was observed. However, cutaneous pruritus relapsed, and ALP level increased again. |

**Laboratory test value**

| | Day 1 of admin. | Day 43 of admin. (day of discon-tinuation) | 1 day after discon-tinuation | 4 days after discon-tinuation | 8 days after discon-tinuation | 12 days after discon-tinuation | 16 days after discon-tinuation | 22 days after discon-tinuation | 26 days after discon-tinuation | 32 days after discon-tinuation | 62 days after discon-tinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| WBC (/μL) | 6 200 | 11 200 | 12 300 | 14 800 | 24 000 | 10 300 | 9 200 | 8 500 | 8 000 | 5 100 | - |
| Eosinophil count (%) | 3.2 | 24.5 | 23.0 | 32.5 | 49.0 | 24.0 | 2.0 | 0.5 | 0 | 0 | - |
| Atypical lymphocytes (%) | - | 0 | - | 0 | 0 | 0.5 | 0 | 1.5 | 2.0 | 0 | - |
| ALP (U/L) | - | 2 298 | 2 562 | 2 337 | 1 491 | 690 | 1 139 | 1 105 | 772 | 537 | 298 |
| AST (IU/L) | 20 | 119 | 102 | - | 44 | - | - | - | - | - | - |
| ALT (IU/L) | 18 | 85 | 83 | - | 46 | - | - | - | - | - | - |
| T-Bil (mg/dL) | 0.7 | 3.3 | 3.3 | - | 1.2 | - | - | - | - | - | - |
| CRP (mg/dL) | - | 4.77 | 4.64 | - | 0.67 | - | - | - | - | - | - |

Suspected concomitant drugs: Goserelin acetate, silodosin, cefcapene pivoxil hydrochloride hydrate
Concomitant drugs: None

## 2 Technetium ($^{99m}$Tc) tetrofosmin

| | |
|---|---|
| **Brand name (name of company)** | Myoview Kit, Myoview Injection (Nihon Medi-Physics Co., Ltd.) |
| **Therapeutic category** | Radioactive medicines |
| **Indications** | Diagnosis of heart disease based on myocardial scintigraphy, diagnosis of cardiac function by first-transit study |

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

| | |
|---|---|
| **[Under new instructions]** | |
| **2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) (newly added)** | Patients with a history of hypersensitivity to any of the ingredients of this drug |
| **11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)** | Shock, anaphylaxis |
| **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 shock, anaphylaxis reported in Japan: 2 (No patient mortalities)<br>Cases involving shock, anaphylaxis reported overseas: 8 (No patient mortalities)<br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 58 000<br>Myoview Kit: April 1994<br>Myoview Injection 296 MBq, 592 MBq: January 1997<br>Myoview Injection 740 MBq: January 1998 |

## Case summary

| No. | Patient | | Daily dose/ administration duration | Adverse reaction |
|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment |
| 1 | Male 70s | ATP-loaded myocardial scintigraphy (none) | 296 MBq Single dose ↓ 740 MBq Single dose | **Anaphylactic shock**<br>Primary disease: Angina on exercise<br>Medical history: Interstitial pneumonia, hypertension<br>History of adverse drug reaction: Allergy to iodinated contrast media<br>History of prior treatment with technetium ($^{99m}$Tc) tetrofosmin: None<br>Before administration: Drug loading with ATP preparations was performed.<br>Day 1 of administration (day of termination): The 1st dose of technetium ($^{99m}$Tc) tetrofosmin 296 MBq was administered (during drug loading).<br>20 minutes after administration of the 1st dose: Urticaria developed on the upper limb and trunk.<br>30 minutes after administration of the 1st dose: 200 mg of hydrocortisone sodium phosphate was administered by intravenous infusion. The symptoms remitted.<br>2 hours and 22 minutes after administration of the 1st dose: The 2nd dose of technetium ($^{99m}$Tc) tetrofosmin 740 MBq was administered (at rest).<br>30 seconds after administration of the 2nd dose: Anaphylactic shock occurred (redness, pruritus, cold sweat, generalised urticaria, erythema, decreased blood pressure, depressed level of consciousness, and urinary incontinence).<br>8 minutes after administration of the 2nd dose: 200 mg of hydrocortisone sodium phosphate was administered by intravenous infusion and 1 ampoule of hydroxyzine hydrochloride by intravenous injection. Both vital signs and the symptoms improved.<br>30 minutes after administration of the 2nd dose: Anaphylactic shock was resolved.<br>1 day after administration: The patient was discharged from the hospital without abnormalities. |

**Laboratory test value**

| | Before administration | 70 minutes after administration of the 1st dose | 1 minute after administration of the 2nd dose | 8 minutes after administration of the 2nd dose |
|---|---|---|---|---|
| Blood pressure (mmHg) | − | 100/71 | 75/− | 123/61 |
| Pulse rate (beats/min) | − | 77 | 82 | 85 |

Concomitant drugs: Adenosine triphosphate disodium hydrate, candesartan cilexetil/amlodipine besilate, amlodipine besilate

# 4
# Revision of PRECAUTIONS (No.345)

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 12, 2023.

## 1 Other agents relating to blood and body fluids
## [1] Filgrastim (genetical recombination)
## [2] Filgrastim (genetical recombination, biosimilar 1)
## [3] Filgrastim (genetical recombination, biosimilar 2)

**Brand name**

[1] Gran Injection 75, 150, M300, Gran Syringe 75, 150, M300 (Kyowa Kirin Co., Ltd.)
[2] Filgrastim BS 75 μg Syringe for Inj. Mochida, 150 μg Syringe for Inj. Mochida, 300 μg Syringe for Inj. Mochida (Mochida Pharmaceutical Sales Co., Ltd.), Filgrastim BS Injection Syringe "F" 75 μg, 150 μg, 300 μg (Fuji Pharma Co., Ltd.)
[3] Filgrastim BS Injection Syringe "NIG" 75 μg, 150 μg, 300 μg (Nichi-Iko Gifu Plant Co., Ltd.), Filgrastim BS Injection 75 μg Syringe "NK", 150 μg Syringe "NK", 300 μg Syringe "NK" (Nippon Kayaku Co., Ltd.)

**[Under old instructions]**

**Important Precautions (newly added)**

Precautions for chemotherapy-induced neutropenia
An observational study performed overseas has reported an increased risk of myelodysplastic syndrome or acute myeloid leukemia in patients with breast or lung cancer who were treated with pegfilgrastim (genetical recombination) or filgrastim (genetical recombination) in conjunction with chemotherapy (monotherapy or combination therapy with radiotherapy). Although the causal relationship of this drug to myelodysplastic syndrome or acute myeloid leukemia is not clear, patients should be carefully monitored after administration of this drug.

**[Under new instructions]**

**8. IMPORTANT PRECAUTIONS (newly added)**

<Chemotherapy-induced neutropenia>
An observational study performed overseas has reported an increased risk of myelodysplastic syndrome or acute myeloid leukemia in patients with breast or lung cancer who were treated with pegfilgrastim (genetical recombination) or filgrastim (genetical recombination) in conjunction with chemotherapy (monotherapy or combination therapy with radiotherapy). Although the causal relationship of this drug to myelodysplastic syndrome or acute myeloid leukemia is not clear, patients should be carefully monitored after administration of this drug.

## 2 Other agents relating to blood and body fluids
## [1] Pegfilgrastim (genetical recombination)
## [2] Pegfilgrastim (genetical recombination, biosimilar 1)

**Brand name**

[1] G-Lasta Subcutaneous Injection 3.6 mg, G-Lasta Subcutaneous Injection 3.6 mg BodyPod (Kyowa Kirin Co., Ltd.)
[2] Pegfilgrastim BS Subcutaneous Injection 3.6 mg "Nipro", Pegfilgrastim BS Subcutaneous Injection 3.6 mg "Mochida" (Mochida Pharmaceutical Co., Ltd.)

**[Under new instructions]**

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS (newly added)** | **<Prevention of chemotherapy-induced febrile neutropenia>**<br>An observational study performed overseas has reported an increased risk of myelodysplastic syndrome or acute myeloid leukemia in patients with breast or lung cancer who were treated with pegfilgrastim (genetical recombination) or filgrastim (genetical recombination) in conjunction with chemotherapy (monotherapy or combination therapy with radiotherapy). Although the causal relationship of this drug to myelodysplastic syndrome or acute myeloid leukemia is not clear, patients should be carefully monitored after administration of this drug. |

3 Other agents relating to blood and body fluids

## Lenograstim (genetical recombination)

| | |
|---|---|
| **Brand name** | Neutrogin for Injection 50 μg, 100 μg, 250 μg (Chugai Pharmaceutical Co., Ltd.) |
| **[Under new instructions]** | |
| **8. IMPORTANT PRECAUTIONS (newly added)** | <Chemotherapy-induced neutropenia><br>An observational study performed overseas has reported an increased risk of myelodysplastic syndrome or acute myeloid leukemia in patients with breast or lung cancer who were treated with pegfilgrastim (genetical recombination) or filgrastim (genetical recombination), which are drugs of the same class, in conjunction with chemotherapy (monotherapy or combination therapy with radiotherapy). Although the causal relationship of this drug to myelodysplastic syndrome or acute myeloid leukemia is not clear, patients should be carefully monitored after administration of this drug. |

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

## Diazoxide

| | |
|---|---|
| **Brand name** | Diazoxide Capsules 25 mg "OP" (OrphanPacific, Inc.) |
| **[Under new instructions]** | |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**<br>**9.7 Pediatric Use** | Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Pericardial effusion and pulmonary hypertension may occur. In addition, necrotizing enterocolitis may occur in neonates. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions** | Serious fluid retention, congestive heart failure, pericardial effusion<br>Serious sodium retention, fluid retention, congestive heart failure and pericardial effusion may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures, such as administration of diuretics, should be taken. |
| **(newly added)** | Necrotising enterocolitis<br>Necrotising enterocolitis may occur in neonates. If symptoms such as vomiting, abdominal distension, diarrhoea, and bloody stool occur, administration of this drug should be discontinued, and appropriate measures should be taken. |

5 Other antitumor agents

## Apalutamide

| | |
|---|---|
| **Brand name** | Erleada Tablets 60 mg (Janssen Pharmaceutical K.K.) |
| **[Under new instructions]** | |

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|---|---|
| **8. IMPORTANT PRECAUTIONS** | Severe skin disorders and drug-induced hypersensitivity syndrome may occur. If a rash occurs, a dermatologist should be consulted at an early stage, and temporary discontinuation or discontinuation of this drug should be considered. Patients should be instructed to immediately seek medical attention if any skin abnormalities are observed. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (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. |

6 Other antitumor agents

## Ipilimumab (genetical recombination)

| | |
|---|---|
| **Brand name** | Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.) |
| **[Under new instructions]** | |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions** | Encephalitis, meningitis |

7 Radioactive medicines

## Technetium ($^{99m}$Tc) tetrofosmin

| | |
|---|---|
| **Brand name** | Myoview Kit, Myoview Injection (Nihon Medi-Physics Co., Ltd.) |
| **[Under new instructions]** | |
| **(newly added)** | 2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)<br>Patients with a history of hypersensitivity to any of the ingredients of this drug |
| **11. ADVERSE REACTIONS (newly added)** | 11.1 Clinically Significant Adverse Reactions<br>Shock, anaphylaxis |

8 Vaccines

## COVID-19 (SARS-CoV-2) vaccine (recombinant chimpanzee adenovirus vector)

| | |
|---|---|
| **Brand name** | Vaxzevria Intramuscular Injection (AstraZeneca K.K.) |
| **[Under new instructions]** | |
| **8. IMPORTANT PRECAUTIONS (newly added)** | Since immune thrombocytopenia has been reported following inoculation with this vaccine, a platelet count test should be performed as necessary. |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS** | Persons with a history of immune thrombocytopenia□The platelet count should preferably be monitored. |

| | |
|---|---|
| **9.1 Persons to Be Vaccinated with Caution (Persons in whom the decision to vaccinate must be made with caution) (newly added)** | |
| **11. ADVERSE REACTIONS** | |
| **11.1 Clinically Significant Adverse Reactions (newly added)** | Immune thrombocytopenia |

9 Agents for not mainly purpose of therapeutic, n.e.c.

## Adenosine

| | |
|---|---|
| **Brand name** | Adenoscan Injection 60 mg (Daiichi Sankyo Co., Ltd.), and the others |
| **[Under old instructions]** | |
| **Adverse Reactions** | |
| **Clinically Significant Adverse Reactions (newly added)** | Anaphylaxis:<br>Cases that led to anaphylactic shock have also been reported. |
| **[Under new instructions]** | |
| **11. ADVERSE REACTIONS** | |
| **11.1 Clinically Significant Adverse Reactions (newly added)** | Anaphylaxis<br>Cases that led to anaphylactic shock have also been reported. |

10 Antipyretics, analgesics and anti-inflammatory agents

## Acetaminophen (oral dosage form)

| | |
|---|---|
| **Brand name** | Calonal powder, Calonal tablets 200, 300, 500, Calonal Fine Gran. 20%, 50%, Calonal Syrup 2% (AYUMI Pharmaceutical Corporation), and the others |
| **[Under old instructions]** | |
| **Contraindications (This drug is contraindicated to the following patients.)** | (deleted) |
| **Precautions for Dosage and Administration (newly added)** | The maximum dose for patients with aspirin asthma or a history of the disease should be 300 mg or less of acetaminophen per dose. |
| **Careful Administration (Careful administration of this drug is required in the following patients.)** | Patients with peptic ulcer or a history of the disease [Symptoms may be exacerbated or recurrence may be promoted.]<br>Patients with blood abnormalities or a history of the disease [Symptoms may be exacerbated or recurrence may be promoted.]<br>Patients with renal disorder or a history of the disease [Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted.]<br>Patients with abnormal cardiac function [Symptoms may be exacerbated or cardiac failure may be aggravated.] |
| **(newly added)** | Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease [It is |

| | |
|---|---|
| | considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and symptoms may be exacerbated or recurrence may be promoted.] |
| **[Under new instructions]**<br>**2.CONTRAINDICATIONS (This drug is contraindicated to the following patients.)** | (deleted) |
| **7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION (newly added)** | The maximum dose for patients with aspirin asthma or a history of the disease should be 300 mg or less of acetaminophen per dose. |
| **9.PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**<br>**9.1 Patients with Complication or History of Diseases, etc.** | Patients with peptic ulcer or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with blood abnormalities or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with abnormal cardiac function<br>Symptoms may be exacerbated or cardiac failure may be aggravated.<br>Patients with bronchial asthma<br>Symptoms may be exacerbated. |
| **(newly added)** | Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease<br>It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and symptoms may be exacerbated or recurrence may be promoted. |
| **9.2 Patients with renal impairment** | (deleted)<br>Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted. |

11 Antipyretics, analgesics and anti-inflammatory agents

## Acetaminophen (injections)

| | |
|---|---|
| **Brand name** | acelio Bag for Intravenous Injection 1000 mg (Terumo Corporation) |
| **[Under new instructions]**<br>**2.CONTRAINDICATIONS (This drug is contraindicated to the following patients.)** | (deleted) |
| **7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION (newly added)** | The maximum dose for patients with aspirin asthma or a history of the disease should be 300 mg or less of acetaminophen per dose. |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**<br>**9.1 Patients with Complication or History of Diseases, etc.** | Patients with peptic ulcer or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with blood abnormalities or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with abnormal cardiac function<br>Symptoms may be exacerbated or cardiac failure may be aggravated.<br>Patients with bronchial asthma<br>Symptoms may be exacerbated. |
| **(newly added)** | Patients with aspirin asthma (induction of asthmatic attack due to |

| | |
|---|---|
| | nonsteroidal anti-inflammatory drug) or a history of the disease<br>It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and the symptoms may be exacerbated or recurrence may be promoted. |
| **9.2 Patients with renal impairment** | (deleted)<br>Patients with renal disorder or a history of the disease<br>Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted. |

12 Antipyretics, analgesics and anti-inflammatory agents

## Acetaminophen (suppository)

| | |
|---|---|
| **Brand name** | Alpiny Suppositories 50, 100, 200 (Hisamitsu Pharmaceutical Co., Inc.), Anhiba pediatric suppository 50 mg, 100 mg, 200 mg (Mylan EPD G.K.), Calonal Supp. 50 for Pediatric, Calonal Supp. 100, 200, 400 (AYUMI Pharmaceutical Corporation), and the others |
| **[Under old instructions]** | |
| **Contraindications (This drug is contraindicated to the following patients.)** | (deleted) |
| **Precautions for Dosage and Administration (newly added)** | The maximum dose for patients with aspirin asthma or a history of the disease should be 300 mg or less of acetaminophen per dose. |
| **Careful Administration (Careful administration of this drug is required in the following patients.)** | Patients with blood abnormalities or a history of the disease [Symptoms may be exacerbated or recurrence may be promoted.]<br>Patients with renal disorder or a history of the disease [Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with abnormal cardiac function [Symptoms may be exacerbated or cardiac failure may be aggravated.] |
| **(newly added)** | Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease [It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and the symptoms may be exacerbated or recurrence may be promoted.] |
| **[Under new instructions]** | |
| **2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)** | (deleted) |
| **7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION (newly added)** | The maximum dose for patients with aspirin asthma or a history of the disease should be 300 mg or less of acetaminophen per dose. |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS** | Patients with blood abnormalities or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with abnormal cardiac function<br>Symptoms may be exacerbated or cardiac failure may be aggravated. |
| **9.1 Patients with Complication or History of Diseases, etc. (newly added)** | Patients with bronchial asthma<br>Symptoms may be exacerbated.<br>Patients with aspirin asthma (induction of asthmatic attack due to |

| | |
|---|---|
| | nonsteroidal anti-inflammatory drug) or a history of the disease<br>It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and the symptoms may be exacerbated or recurrence may be promoted. |
| **9.2 Patients with renal impairment** | (deleted)<br>Patients with renal disorder or a history of the disease<br>Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted. |

13 Antipyretics, analgesics and anti-inflammatory agents

## Tramadol hydrochloride/acetaminophen

| | |
|---|---|
| **Brand name** | Tramcet Combination Tablets (Janssen Pharmaceutical K.K.), and the others |
| **[Under old instructions]** | |
| **Contraindications (This drug is contraindicated to the following patients.)** | (deleted)<br>Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) who have pain after tooth extraction [It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma.] |
| **Precautions for Dosage and Administration (newly added)** | When this drug is administered to patients with aspirin asthma or a history of the disease who have chronic pain, the dose should be one tablet per dose. |
| **Careful Administration (Careful administration of this drug is required in the following patients.)** | Patients with liver disorder or a history of the disease [Liver function may worsen. Also, the drug concentration in blood may remain high and the effect and adverse reactions may be enhanced.]<br>Patients with renal disorder or a history of the disease [Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted. Also, the drug concentration in blood may remain high and the effect and adverse reactions may be enhanced.]<br>Patients with peptic ulcer or a history of the disease [Symptoms may be exacerbated or recurrence may be promoted.]<br>Patients with blood abnormalities or a history of the disease [Symptoms may be exacerbated or recurrence may be promoted.]<br>Patients with abnormal cardiac function [Symptoms may be exacerbated or cardiac failure may be aggravated.] |
| **(newly added)** | Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease who have chronic pain [Adjusting the dose using not this drug but single active ingredient preparations containing acetaminophen should be considered. The maximum dose of acetaminophen for patients with aspirin asthma or a history of the disease should be 300 mg or less per dose. However, this drug contains 325 mg of acetaminophen per tablet. It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and the symptoms may be exacerbated or recurrence may be promoted.] |
| **[Under new instructions]** | |
| **2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)** | <Common to all indications><br>(deleted)<br><Pain after tooth extraction><br>Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease [It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma.] |

| | |
|---|---|
| **7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION <Non-cancerous chronic pain> (newly added)** | When this drug is administered to the patients with aspirin asthma or a history of the disease, the dose should be one tablet per dose. |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)** | <Common to all indications><br>Patients with peptic ulcer or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with blood abnormalities or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with abnormal cardiac function.<br>Symptoms may be exacerbated or cardiac failure may be aggravated.<br><Non-cancerous chronic pain><br>Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease<br>Adjusting the dose using not this drug but single active ingredient preparations containing acetaminophen should be considered. The maximum dose of acetaminophen for patients with aspirin asthma or a history of the disease should be 300 mg or less per dose. However, this drug contains 325 mg of acetaminophen per tablet. It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and the symptoms may be exacerbated or recurrence may be promoted. |
| **9.2 Patients with renal impairment** | (deleted)<br>Patients with renal disorder or a history of the disease<br>Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted. Also, the drug concentration in blood may remain high and the effect and adverse reactions may be enhanced. |

## 14 Antitussives

## Diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/ acetaminophen/bromovalerylurea

| | |
|---|---|
| **Brand name** | Coughcode-N Combination Tablets (Mylan EPD G.K.) |
| **[Under new instructions]** | |
| **2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)** | (deleted) |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)** | Patients with abnormal cardiac function<br>Symptoms may be exacerbated or cardiac failure may be aggravated.<br>Patients with peptic ulcer or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with blood abnormalities or a history of the disease<br>Symptoms may be exacerbated or recurrence may be promoted.<br>Patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease |

| | |
|---|---|
| | It is considered that the inhibitory activity of prostaglandin synthesis is involved in the onset of aspirin asthma, and the symptoms may be exacerbated or recurrence may be promoted. |
| **9.2 Patients with renal impairment** | (deleted)<br>Patients with renal impairment or a history of the disease<br>Dose reduction and prolongation of dosing intervals should be considered. Symptoms may be exacerbated or recurrence may be promoted. |

# 5

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

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

(As of September 30, 2023)
◎: Products for which EPPV was initiated after September 1, 2023

| | Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | Ritlecitinib tosilate<br>Litfulo Capsules 50 mg | Pfizer Japan Inc. | September 27, 2023 |
| ◎ | Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)<br>Comirnaty intramuscular injection for 6 months to 4 years old | Pfizer Japan Inc. | September 26, 2023 |
| ◎ | Tralokinumab (genetical recombination)<br>Adtralza S.C. Injection 150 mg Syringe | LEO Pharma K.K. | September 26, 2023 |
| ◎ | Dupilumab (genetical recombination)<br>[1] Dupixent S.C. Injection 200 mg Syringe,<br>[2] Dupixent S.C. Injection 300 mg Syringe,<br>[3] Dupixent S.C. Injection 300 mg Pen | Sanofi K.K. | September 25, 2023 |
| ◎ | Lenacapavir sodium<br>Sunlenca Subcutaneous Injection 463.5 mg, Sunlenca Tablets 300 mg | Gilead Sciences K.K. | September 13, 2023 |
| ◎ | Futibatinib<br>Lytgobi tablets 4 mg | TAIHO Pharmaceutical Co., Ltd. | September 7, 2023 |
| ◎ | Pegcetacoplan<br>Empaveli for Subcutaneous Injection 1080 mg | Swedish Orphan Biovitrum Japan Co., Ltd. | September 4, 2023 |
| | Eculizumab (genetical recombination)<br>Soliris for Intravenous Infusion 300 mg | Alexion Pharma Godo Kaisha | August 23, 2023 |
| | Ruxolitinib phosphate[*1]<br>Jakavi Tablets 5 mg, 10 mg | Novartis Pharma K.K. | August 23, 2023 |
| | Coronavirus modified uridine RNA vaccine (SARS-CoV-2)<br>Spikevax Intramuscular Injection | Moderna Japan Co., Ltd. | August 2, 2023 |
| | Purified pineapple stem juice | Kaken Pharmaceutical | August 1, |

| Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| NexoBrid gel 5 g | Co., Ltd. | 2023 |
| Foslevodopa/foscarbidopa hydrate<br>Vyalev combination subcutaneous infusion | AbbVie GK | July 26, 2023 |
| Anti-human thymocyte immunoglobulin, equine<br>Atgam Intravenous Infusion 250 mg | Pfizer Japan Inc. | July 24, 2023 |
| Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) [*2]<br>Vaxneuvance Aqueous Suspension Syringes | MSD K.K. | June 26, 2023 |
| Febuxostat<br>Feburic Tablets 10 mg, 20 mg, 40 mg | Teijin Pharma Limited. | June 26, 2023 |
| Somapacitan (genetical recombination) [*3]<br>Sogroya Subcutaneous Injection 5 mg, 10 mg, 15 mg | Novo Nordisk Pharma Ltd. | June 26, 2023 |
| Mirikizumab (genetical recombination)<br>Omvoh Intravenous Infusion 300 mg, Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes | Eli Lilly Japan K.K. | June 21, 2023 |
| Cholic acid<br>Orphacol Capsules 50 mg | ReqMed Company, Ltd. | June 19, 2023 |
| Vedolizumab (genetical recombination)<br>Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg | Takeda Pharmaceutical Company Limited. | June 19, 2023 |
| Crisantaspase<br>Erwinase for intramuscular injection 10000 | Ohara Pharmaceutical Co., Ltd. | June 14, 2023 |
| Tirzepatide<br>Mounjaro Subcutaneous Injection Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos | Eli Lilly Japan K.K. | June 12, 2023 |
| Ropeginterferon alfa-2b (genetical recombination)<br>*Besremi* Subcutaneous Injection Syringes 250 μg, 500 μg | PharmaEssentia Japan KK | June 1, 2023 |
| Oxybutynin hydrochloride [*4]<br>Apohide Lotion 20% | Hisamitsu Pharmaceutical Co., Inc. | June 1, 2023 |
| Avatrombopag maleate<br>Doptelet tablets 20 mg | Swedish Orphan Biovitrum Japan Co., Ltd. | June 1, 2023 |

| | Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| | Pegvaliase (genetical recombination)<br>Palynziq Subcutaneous Injection 2.5 mg, 10 mg, 20 mg | BioMarin Pharmaceutical Japan K.K. | May 24, 2023 |
| | Mifepristone/misoprostol<br>Mefeego Pack | Linepharma KK | May 16, 2023 |
| | Treprostinil<br>Treprost Inhalation Solution 1.74 mg | Mochida Pharmaceutical Co., Ltd. | May 16, 2023 |
| | Tirzepatide<br>Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos | Eli Lilly Japan K.K. | April 18, 2023 |
| | Edaravone<br>Radicut Ors 2.1% | Mitsubishi Tanabe Pharma Corporation | April 17, 2023 |
| | Donepezil<br>Allydone Patches 27.5 mg, 55 mg | Teikoku Seiyaku Co., Ltd. | April 14, 2023 |
| | Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)<br>Vaxneuvance Aqueous Suspension Syringes | MSD K.K. | April 10, 2023 |
| | Isavuconazonium sulfate<br>Cresemba Capsules 100 mg, Cresemba for i.v. infusion 200 mg | Asahi Kasei Pharma Corporation | April 6, 2023 |
| | Fostamatinib sodium hydrate<br>Tavalisse Tablets 100 mg, 150 mg | Kissei Pharmaceutical Co., Ltd. | April 6, 2023 |

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

*2 Prevention of invasive disease caused by *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in children

*3 Growth hormone-deficient short stature without epiphyseal closure

*4 Primary palmar hyperhidrosis