Pharmaceuticals and Medical Devices Safety Information

No. 396

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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) Medical Product Information 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 MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

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

Pharmaceuticals and Medical Devices Safety Information

No. 396

Ministry of Health, Labour and Welfare
Pharmaceutical Safety and Environmental Health 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 medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

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
CSF	Cerebrospinal Fluid
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
ODID	Office of Drug Induced Damages
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive Multifocal Leukoencephalopathy
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SD	Safety Division
SYB	Sports and Youth Bureau
TEN	Toxic Epidermal Necrolysis

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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 Infections Derived from Biological Products Relief System, 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 vaccinations such as novel coronavirus vaccine in accordance with the Preventative Vaccination Law are not covered by the Relief System, but by the Relief System for Injury to Health with Vaccination. However, adverse health effects resulting from voluntary vaccinations are eligible for relief under the Relief System.

In the Relief System, a total of 27 609 cases have been granted relief benefits since its establishment in 1980 until the end of fiscal year (FY) 2021. 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 should provide information on the Relief System and cooperate with the preparation of medical certificates, etc. required for claim of 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 (serious 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, 2022)]
Medical Expenses (costs borne by the patients, not including health insurance payments)
• Actual costs of treatment for the disease caused by ADRs will be compensated.
Medical Allowance (34 900 to 36 900 yen per month)
• Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs.

[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)

Disability Pension (Grade 1: 2 804 400 yen per year, Grade 2: 2 244 000 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: 877 200 yen per year, Grade 2: 702 000 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 (2 452 800 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 (7 358 400 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 for Adverse Drug Reactions

Awareness of the Relief System among the general public in FY 2021 was 33.8% in total according to the FY 2021 survey: 10.2% answered that they “were aware” of the Relief System and 23.6% 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 82.6% in total: 62.4% answered that they “were aware” of the Relief System and 20.2% answered that they “have heard about” the Relief System. By occupational category, awareness was 92.5% among physicians, 97.0% among pharmacists, 59.9% among nurses, and 84.2% 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 13.6% overall: 16.9% among physicians, 16.0% among pharmacists, 5.7% among nurses, and 13.5% among dentists [Note 1)].

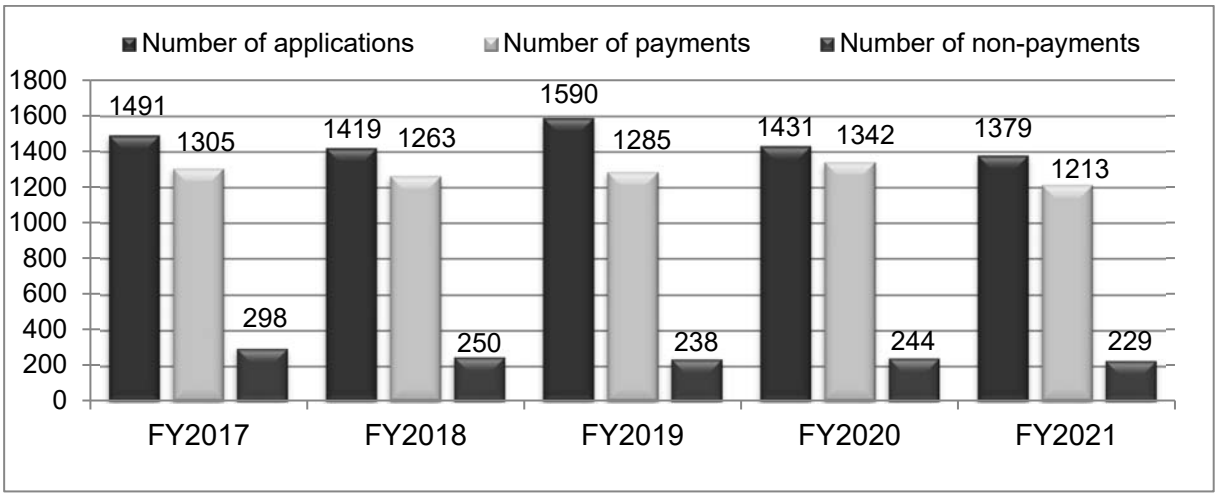
Furthermore, in all application forms related to relief benefits, the input field for “the source of information related to the Relief System” (selected from “Physician,” “Dentist,” “Pharmacist,” “Other medical facility staff,” “Newspaper/TV, etc.” and “Others”) was newly included in April 2016 to grasp the sources of information related to the Relief System. The FY 2021 results showed “Physician” in 478 answers (32.6%), “Others” (the Internet) in 288 answers (19.6%), “Pharmacist” in 172 answers (11.7%) in descending order (multiple answers acceptable). [Note 2]

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

The annual numbers of applications and payments in the Relief System between FY 2017 and FY 2021 are shown in Figure 1. In FY2021, the number of applications was 1 379, the number of payments was 1 213, and the number of non-payments was 229. The ratios between payment and non-payment and details of reasons for non-payments from FY 2017 to FY 2021 are shown in Figure 2.

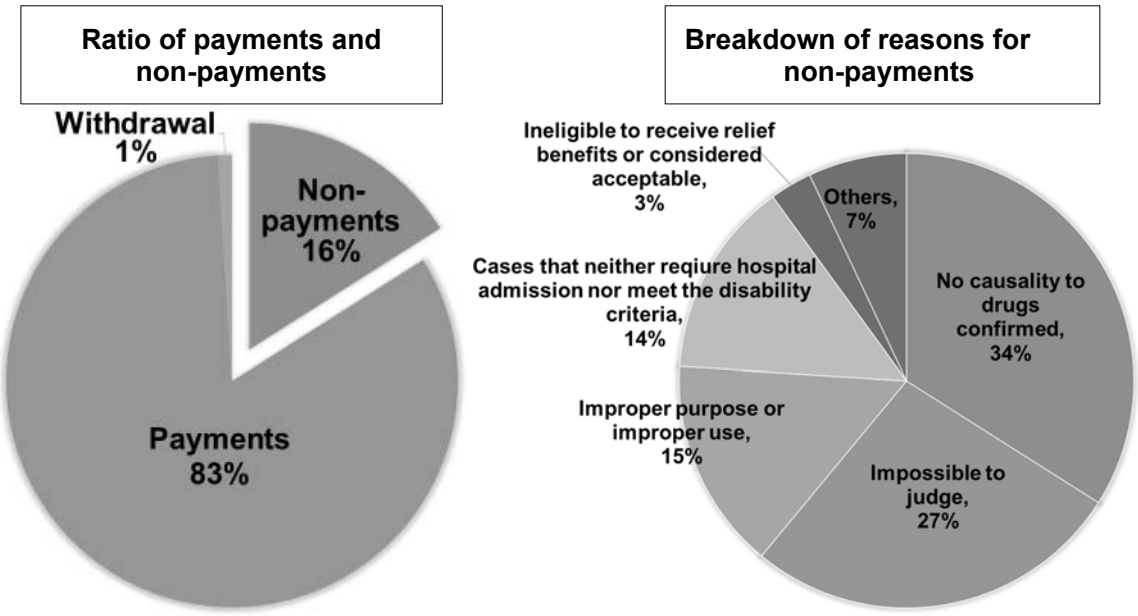
In addition, the standard administrative processing time [Note 3)] from when PMDA receives an application to when the agency notifies the applicant of the decision was set at within 6 months, and the goal is to achieve the standard administrative processing time in 60% or more of cases for which payment or non-payment was determined. The actual achievement percentage in FY 2021 was 83.2%, which was the highest result greatly exceeding 60%.

Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2017 to FY 2021)



(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 2017 and FY 2021



5. Cases of relief benefit payments/non-payments

5.1 Cases of relief benefit payments

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

A male under 10 years old. He developed thrombocytopenic purpura following vaccination of Influenza HA vaccine "Seiken" and received inpatient treatment. Medical allowance benefits were provided.

<Case 2> A case of fulminant hepatitis due to telmisartan, for which medical expenses, medical allowance, bereaved family benefits, and funeral expenses benefits were provided

A male in his 60s. He developed fulminant hepatitis after using Telmisartan Tablets 40 mg "Nichi-iko" and received inpatient treatment. Subsequently, he died. Medical expenses, medical allowance benefits, bereaved family benefits, and funeral expenses benefits were provided.

<Case 3> A case in which cerebral infarction due to norethisterone/ethinylestradiol led to a disability status, for which medical expenses, medical allowance benefits, bereaved family benefits were provided

A female in her 40s. She experienced cerebral infarction following use of Lunabell tablets ULD (norethisterone/ethinylestradiol) and received inpatient treatment. She had functional disorder in the extremities/higher brain dysfunction secondary to cerebral infarction. Medical expenses, medical allowance, and disability pension benefits were provided.

<Case 4> A case of anaphylaxis due to an OTC drug, for which medical expenses and medical allowance benefits were provided.

A male in his 50s. He experienced anaphylaxis following use of Bufferin A 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 1 259[Note 4)] non-payment cases from FY 2017 to FY 2021, the reason for non-payment in approximately 15% 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 2017 to FY 2021)

Name of causative drug	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	Total (cases)
Lamotrigine	9	12	15	8	5	49
Thiamazole	1	3	2	4	2	12
Methotrexate	1	1	4	5	1	12
Lithium carbonate	0	1	3	0	3	7
Human chorionic gonadotropin	0	0	1	2	4	7
Loxoprofen sodium	1	2	1	0	3	7
Others	16	25	20	16	19	96
Total (cases)	28	44	46	35	37	190

(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 drugs.

<Case 1> A case of erythema multiforme type drug eruption due to lamotrigine (when titrating)

A female in her 40s. She used Lamotrigine Tablets 25 mg "JG" for recurrence of mood episodes for bipolar disorder with sodium valproate. Lamotrigine was started on alternate days at a dose of 25 mg, which was increased to 25 mg/day after 7 days, and to 50 mg/day after 14 days of administration. Therefore, this drug use was not considered proper.

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

A female in her 60s. She used Lamictal Tablets for bipolar disorder with drugs other than those inducing glucuronidation. The administration of lamotrigine was started at a daily dose of 50 mg, which was increased to 100 mg/day after 7 days. 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 PMDA issued the Alert for Proper Use of Drugs in January 2012[Note 5)] 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. PMDA issued the Alert for Proper Use of Drugs in October 2019[Note 6)] 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 an earlier dose increase.

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 episode 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)

	Concomitant medication			
Concomitant drugs with lamotrigine	(2) With sodium valproate	(3) Without sodium valproate[*1]		(1) Lamotrigine monotherapy
		(3)-i) With drugs that induce glucuronidation of lamotrigine[*2]	(3)-ii) With drugs other than (3)-i)[*3]	
Week 1/2	25 mg/day every 2 days	50 mg/day (once daily)	25 mg/day (once daily)	
Week 3/4	25 mg/day (once daily)	100 mg/day (twice daily in divided doses)	50 mg/day (once or twice 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 1 week or longer apart.)	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 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 agranulocytosis due to thiamazole

A female in her 30s. Since no blood tests including differential count of leukocytes had been conducted for 27 days until agranulocytosis was observed after the start of Mercazole Tablets (thiamazole) administration, the case was not approved as proper use.

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

Warnings

It has been reported that serious agranulocytosis mainly developed within 2 months after the start of administration, resulting in death in some cases. In principle, a blood test including differential count of leukocytes should be performed once every 2 weeks for at least 2 months after the start of administration and periodically thereafter. If any abnormalities such as decreasing tendency of granulocytes are observed, administration should be discontinued immediately and appropriate measures should be taken. Similar caution is required when resuming administration after discontinuing this drug.

<Case 2> A case of pancytopenia due to salazosulfapyridine

A female in her 70s. Since no blood tests including differential count of leukocytes had been performed for 43 days until pancytopenia was observed after the start of Salazosulfapyridine Tablets 500 mg "Taiyo" administration, the case was not approved as proper use.

Description in the electronic package insert of Salazosulfapyridine Tablets 500 mg "Taiyo" (revised in May 2020) (partial excerpt)

Important Precautions

Before administration of this drug, it should be ensured that a haematological test (haemogram including differential leukocyte count) and liver and renal function tests were performed.

Patients should be carefully monitored for changes in their clinical symptoms during treatment with this drug and periodic haematological and liver function tests should be performed (once every 2 weeks in the first 3 months, once every 4 weeks in the next 3 months and once every 3 months after 6 months of administration in principle). Periodic renal function tests should also be performed.

<Case 3> A case of lithium poisoning due to lithium carbonate

A male in his 50s. Administration of lithium carbonate tablets 200 mg "Fujinaga" was started. Since no lithium serum concentration had been measured for approximately 8 months until lithium poisoning was observed after the dose of lithium carbonate was increased from 600 mg/day to 800 mg/day, the case was not approved as proper use.

Description in the electronic package insert of Lithium Carbonate Tablets 200 mg "Fujinaga" (revised in August 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.

(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 erythema multiforme due to Daiphen Tablets

A male in his 10s. Although discontinuation of Daiphen Tablets (sulfamethoxazole/trimethoprim) was instructed at the occurrence of erythema, which was suspected to be an adverse drug reaction of Daiphen Tablets by the physician, the patient continued its use at his own discretion ignoring the physician's instruction. Therefore, 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 prescribed again to patients falling under the CONTRAINDICATIONS with a history of adverse drug reactions to it, and the method of use was not considered proper.

Healthcare professionals are strongly requested to adequately consider patients' history of allergies, adverse reactions, or medication in other medical institutions in order to use drugs properly.

<Case> A case where Sawacillin Capsules were used in a patient with a history of allergy

A male in his 30s. Sawacillin Capsules (amoxicillin) was used for the purpose of *Helicobacter pylori* eradication. Although there was a description about a history of allergic dermatitis (urticaria) due to Sawacillin in his medical record at the start of administration, Sawacillin was prescribed and urticaria was observed in prothorax, back, and both thighs approximately 5 days after the prescription. Therefore, the case was not approved as proper use.

Description in the electronic package insert of Sawacillin Capsules (revised in November 2021) (partial excerpt)

2. CONTRAINDICATIONS 2.1 Patients with a history of hypersensitivity to any of the ingredients of this drug

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/english/safety/info-services/drugs/properly-use-alert/0001.html

6. Source of information on Relief System for Adverse Drug Reactions

Details of the Relief System as well as the Infections Derived from Biological Products Relief System 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 website, 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.

http://www.pmda.go.jp/relief-services/adr-sufferers/0004.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 in accordance with 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 7)]
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 8)]
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 9)]:

   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 10)]
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. 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).

• 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 2021 Awareness Survey on the Relief System for Adverse Drug Reaction
https://www.pmda.go.jp/relief-services/adr-sufferers/0023.html (only in Japanese)

Note 2) From: FY 2022 Relief Service Committee (Pharmaceuticals and Medical Devices Agency)
https://www.pmda.go.jp/about-pmda/advisory-council-information/relief-services/0055.html (only in Japanese)

Note 3) 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 4) 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 5) 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 6) Serious Skin Disorders with Lamotrigine and Adherence to Dosage and Administration
https://www.pmda.go.jp/files/000231989.pdf

Note 7) “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 8) Cases where the sufferer’s acceptance of the ADR that occurred is a socially accepted concept.

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

Note 9) Drugs not eligible for relief benefits
https://www.pmda.go.jp/relief-services/adr-sufferers/0044.html (only in Japanese)

Note 10) 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 Human Papillomavirus Vaccine by Relief System for Adverse Drug Reactions

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, MHLW/PMDA have promptly reviewed the relief claims for claimants who claim adverse health effects for symptoms that occurred after administration of HPV vaccines and have taken efforts to increase awareness of the Relief System. By the end of March 2022, 319 of the total 536 patients reviewed had been acknowledged as eligible for the relief because a causal relationship between HPV vaccines and health effects was reasonably possible.

Adverse health effects in people who were vaccinated with vaccines under the “Urgent Vaccination Promotion such as for cervical cancer vaccines” Note) from November 26, 2010 to March 31, 2013 may be regarded to be ADRs based on the review results of the relief benefits. For example, even if the medical care required was not of an extent to be considered inpatient care, such as when patients received treatment on an outpatient basis, the patient may be eligible to receive support for medical expense/medical allowance payments from the Public Foundation of the Vaccination Research Center.

If support for medical expenses/medical allowances is to be provided for the first time for any adverse health effect caused by 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 are first-year junior high school students (approximately 13 years old) up to those who are 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)

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

2. Results of Health Damage Relief through Relief System for Adverse Drug Reactions

The results (annual trends) of health damage relief through the Relief System for Adverse Drug Reactions for 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	0	5 cases	9 cases	8 cases	4 cases	75 cases	314 cases
Fiscal Year	2017	2018	2019	2020	2021	Total	
Number of claims	141 cases	86 cases	59 cases	34 cases	20 cases	909 cases	
Number of Payments	223 cases	111 cases	75 cases	49 cases	29 cases	902 cases	

(Source: PMDA Annual Report FY 2021)
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 for Adverse Drug Reactions in relation to HPV vaccines, etc.

The MHLW issued an administrative notice in 2016 regarding 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 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 vaccination coupons provided prior to vaccination or other reference materials (such as body temperature results, items asked for during the medical interview or examination) and attach these to the claims.

From the administrative notice issued on January 14, 2016 by the Safety Division of the 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 of the Health Service Bureau, MHLW and the Director 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 Based on "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 based on “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 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 Pemafibrate

1. Introduction

Pemafibrate (brand name: Parmodia Tab. 0.1 mg) is a PPARα agonist with triglyceride (TG)-lowering and other effects, which was approved for marketing with the indication for “hyperlipidemia (including familial).” At present, it is not marketed overseas. Administration to “patients with renal impairment whose serum creatinine value is greater than or equal to 2.5 mg/dL or creatinine clearance is less than 40 mL/min” has been specified as a contraindication.

Recently, the language concerning contraindications, etc., for pemafibrate has been revised based on the deliberation in the 13th fiscal year (FY) 2022 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 September 27, 2022. This section will introduce the details of the revision.

2. Background

While other existing fibrates such as fenofibrate and bezafibrate are renally excreted, pemafibrate is known to have a pharmacokinetic profile in which it is metabolized in the liver and excreted mainly in bile. At the marketing authorization approval review for pemafibrate, it was deemed appropriate to provide similar precautions as with existing fibrates based on the following:

- Elevated exposure was observed in subjects with renal impairment compared to subjects with normal renal function.
- In clinical studies in Japan, adverse events such as renal impairment and myalgia have been reported in patients administered with this drug. The incidence of adverse events related to rhabdomyolysis was higher in patients with renal impairment compared to the overall population.

Thereafter, in response to a request from the Japan Atherosclerosis Society (hereinafter referred to as “the Society”), the MAH of pemafibrate conducted the post-marketing clinical study in patients with renal impairment, using eGFR as the index of renal function in the inclusion criteria (hereinafter referred to as “the Study”). Recently, the MAH of pemafibrate has consulted with the PMDA on the revision of the package insert on the basis of the study results (hereinafter referred to as “Revision Consultation”).

In August, 2022, the Society submitted a request to the MHLW for deletion of the language concerning contraindications, etc. for pemafibrate in patients with renal impairment, based on the newly acquired knowledge from the Study.

Given such a background, the Subcommittee on Drug Safety discussed a revision of the precautions.

3. The result of Revision Consultation

In the Revision Consultation, PMDA made the following decisions.

“In the Study, it was observed that the exposure of pemafibrate in patients with severe renal impairment was not higher than that in patients with less severe renal impairment (“2.1 Results of Pharmacokinetics” in Appendix 1[*1]); the occurrence of adverse events related to rhabdomyolysis in the Study and reported post-marketing was evaluated (“2.2 Safety Results” and “3 Post-Marketing Safety Information” in Appendix 1). Based on these, PMDA considered it appropriate that administration to patients with severe renal impairment should not remain contraindicated.

Therefore, it is acceptable to revise the package insert of this drug as shown in Appendix 2[*2], including deleting “patients with renal impairment whose serum creatinine value is greater than or equal to 2.5 mg/dL or creatinine clearance is less than 40 mL/min” from the contraindications.

However, since the number of cases in which this drug has been administered to patients with severe renal impairment is limited, PMDA considered that it is necessary for the MAH to collect information on the relationship between severe renal impairment and adverse events related to rhabdomyolysis and to report such information in the periodic safety update report."

(*1) Appendix 1 "Consultation on the revision of the package insert for Parmodia Tab. 0.1 mg (Kowa Company, Ltd.)" in Material 3-2 of the 13th FY 2022 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on September 27, 2022)

(*2) Appendix 2 "Old/New Comparative Table" in Material 3-2 of the 13th FY 2022 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on September 27, 2022)

4. Deliberation by the Subcommittee on Drug Safety

In light of the result of the Revision Consultation, it was concluded that the following revisions regarding pemafibrate are acceptable, as proposed by the MAH in the Revision Consultation.

- "Patients with renal impairment whose serum creatinine value is greater than or equal to 2.5 mg/dL or creatinine clearance is less than 40 mL/min" should be deleted from the CONTRAINDICATIONS section.
- In addition to listing such patients with severe renal impairment in the Careful Administration section, a cautionary statement should be provided in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" that "the maximum daily dose should be limited to 0.2 mg" for such patients. Of note, the index of renal impairment will be set by eGFR, and patients with severe renal impairment will be defined as those with eGFR less than 30 mL/min/1.73 m^2 based on the inclusion criteria in the Study.

5. Closing remark

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the electronic package insert for a careful decision on the use of pemafibrate. Continued cooperation by healthcare professionals for proper use of this drug would be appreciated.

[References]

・Materials 3-1 to 3-4 of the 13th FY 2022 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on September 27, 2022)
https://www.mhlw.go.jp/stf/newpage_28092.html (only in Japanese)

・Revision of Precautions (PSEHB/PSD Notification No. 1012-3 dated October 12, 2022)
https://www.pmda.go.jp/files/000248516.pdf (only in Japanese)
English translation by PMDA (October 12, 2022)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html

3 Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated October 12, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Methotrexate

Brand name (name of company)	a. Rheumatrex Capsules 2 mg (Pfizer Japan Inc.), and the others b. Methotrexate Tablets 2.5 mg (Pfizer Japan Inc.) c. Methotrexate Injection 200 mg, 1000 mg (Pfizer Japan Inc.) d. Methotrexate Parenteral 5 mg (Pfizer Japan Inc.) e. Methotrexate Parenteral 50 mg (Pfizer Japan Inc.)
Therapeutic category	Agents affecting metabolism, n.e.c. (not elsewhere classified), antimetabolic agents
Indications	a. ·Rheumatoid arthritis ·Treatment of psoriasis vulgaris in patients who have had an inadequate response to local therapies ·Psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis ·Juvenile idiopathic arthritis associated with arthritic symptoms b. Remission of signs and symptoms of the following diseases ·Acute leukaemia ·Trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole) ·Chronic lymphocytic leukaemia ·Chronic myeloid leukaemia c. Methotrexate and leucovorin rescue therapy: ·Sarcomas (bone sarcomas, soft tissue sarcomas, etc.) ·Remission of leukaemic infiltration of central nervous system or testicles in patients with acute leukaemia ·Remission of malignant lymphoma infiltration of central nervous system d. <Conventional therapy with methotrexate> Remission of signs and symptoms of the following diseases ·Acute leukaemia ·Chronic lymphocytic leukaemia ·Chronic myeloid leukaemia ·Trophoblastic disease (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole) <Cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy> ·Breast cancer <Methotrexate plus vinblastine, doxorubicin, and cisplatin (M-VAC) therapy> ·Urothelial carcinoma e.

	<Conventional therapy with methotrexate> Remission of signs and symptoms of the following diseases: ·Acute leukaemia ·Chronic lymphocytic leukaemia ·Chronic myeloid leukaemia ·Trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, and hydatidiform mole) <CMF chemotherapy> ·Breast cancer <Methotrexate and folinate rescue therapy> ·Sarcomas (bone sarcomas, soft tissue sarcomas, etc.) ·Remission of leukaemic infiltration of central nervous system or testicles in patients with acute leukaemia ·Remission of malignant lymphoma infiltration of central nervous system <Sequential methotrexate and fluorouracil therapy> ·Enhancement of antitumor effect of fluorouracil against gastric cancer <M-VAC therapy> ·Urothelial carcinoma

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse reactions **Clinically Significant Adverse Reactions (newly added)**	Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leukoencephalopathy (PML) may occur. Patients should be carefully monitored during and after the treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia or quadriplegia), dyslalia, or speech loss are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and appropriate measures should be taken.

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Progressive multifocal leukoencephalopathy (PML) Patients should be carefully monitored during and after the treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia or quadriplegia), dyslalia, or speech loss are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period Cases involving PML: 6 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: a. Approximately 110 000 b. Approximately 43 496 c. 200 mg preparations: Approximately 9 968, 1000 mg preparations: Approximately 5 350 d. Approximately 13 271 e. Approximately 5 127 Japanese market launch: a. August 1999 b. March 1963 c. 200 mg preparations: August 1988, 1000 mg preparations: February 2013

d. April 1968
e. August 1968

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 70s	Rheumatoid arthritis (gait disturbance)	12 mg (dose per week) Approximately 9 years	**Progressive multifocal leukoencephalopathy** Approximately 17 years before administration: The anti-cyclic citrullinated peptide (anti-CCP) antibody was positive. Administration of prednisolone 1 to 5 mg/day was initiated. Day 1 of administration: Administration of methotrexate 12 mg/week was initiated. Approximately 10 years after administration (day of hospitalization): The patient was hospitalized due to progressive gait disturbance for 5 months and progressive nausea for 1 month. Ataxic dysarthria, pyramidal tract sign on the left side, mild left hemiparesis, marked ataxia in the left upper and lower extremities were noted in the neurological examination at the time of hospital admission. The MRI findings at the time of hospital admission revealed several high signal lesions in the T2W1/FRAIR image in the infratentorial regions including bilateral cerebellar peduncles, cerebellar white matter, and basilar pons. Date unknown (during hospitalization): The patient's clinical condition was aggravated, and methotrexate and prednisolone were tapered and discontinued. Stereotaxic brain biopsy was performed. She was diagnosed with progressive multifocal leukoencephalopathy based on MRI findings and a positive PCR result on cerebrospinal fluid (CSF) examination. Treatment with mefloquine and mirtazapine was initiated. Two months after the treatment initiation, her symptoms showed a tendency to improve. She was discharged from the hospital. Date unknown (5 months after hospital discharge): PCR test results for CSF were undetectable. No exacerbation of symptoms or enlargement of lesions was observed.

Laboratory test value

	Before admin. of methotrexate	Approximately 10 years after admin. (day of hospitalization)	Unknown date before discontinuation (during hospitalization)	Unknown date after discontinuation (during hospitalization)	Approximately 2 months after discontinuation (after hospital discharge)	Unknown date after discontinuation (5 months after hospital discharge)
CSF-JCV-DMA (copies/mL)	-	-	-	2 124	886	undetectable
CD4/CD8 ratio (peripheral blood lymphocyte)	-	-	-	1.6	2.6	-
IgG index	-	2.27	-	1.67	1.69	1.79
SARA* score (point)	-	22	25	-	17	-

*Scale for the Assessment and Rating of Ataxia

Concomitant drugs: Prednisolone

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 60s	Arthritis rheumatoid (none)	6 mg (dose per week) Approximately 4 years ↓ 4 mg (dose per week) Approximately 4 years	**Progressive multifocal leukoencephalopathy, cryptococcal meningitis**	
				Day 1 of administration	The patient was diagnosed with arthritis rheumatoid, and administration of methotrexate 6 mg/week and prednisolone 3 mg/day was initiated.
				Approximately 4 years after administration	Administration of infliximab was initiated, and the dose of prednisolone was reduced to 2 mg/day. Due to remission of rheumatoid arthritis symptoms, the dose of methotrexate was reduced to 4 mg/day and the dose of prednisolone to 1 mg/day.
				Approximately 7 years after administration	Due to remission of rheumatoid arthritis symptoms, prednisolone was discontinued.
				Approximately 8 years after administration (day of hospitalization)	The patient was admitted to the hospital due to transient acute upper and lower extremities weakness and gait disturbance. She was awake and well oriented. No injury was observed in the cranial nerve function, and her cognitive functions were normal. She had numbness in her right fingers. The head CT scan did not reveal any haemorrhagic transformation. Head MRI findings did not reveal any abnormal intensity area in the diffusion weighted image. Nonspecific lesion was found in the FLAIR image.
				Date unknown (2 days after hospitalization)	The result of neurological examination was normal. The patient was diagnosed with transient ischaemic attack.
				Date unknown (5 days after hospitalization)	The patient had no recurrence of quadriplegia and the symptoms of transient ischaemic attack. She was discharged from the hospital.
				Date unknown (8 weeks after hospitalization) (Day of discontinuation)	The patient was rehospitalized due to headache, nausea, dizziness, weight loss, and diplopia. She had mild cognitive dysfunction, and drowsiness and bilateral sixth nerve paralysis were observed in the neurological examination. Deep tendon reflexes of upper and lower limbs were mildly increased, and she was not able to walk without assistance due to headache, dizziness, and diplopia. Cryptococcal antigen was detected in CSF and serum, and *Cryptococcus neoformans* was identified. Head MRI findings revealed a localized lesion in the white matter of the bilateral frontal lobe and temporal lobe. She was diagnosed with cryptococcal meningitis based on the examination of the CSF. Administration of methotrexate and infliximab was discontinued. Induction therapy with amphotericin B and flucytosine was initiated.
				3 weeks after discontinuation (3 weeks after rehospitalization)	The presence of JC virus DNA was detected in the CSF. The patient was diagnosed with suspected PML based on the MRI findings and the results of PCR.
				4 weeks after discontinuation (4 weeks after rehospitalization)	MRI findings revealed enlargement of some lesions and new lesions. No localized neurological symptoms were observed.
				8 weeks after discontinuation	Antifungal maintenance therapy with fluconazole was continued. The patient's

			(8 weeks after rehospitalization) 16 weeks after discontinuation (2 months after the patient was discharged from the rehospitali-zation)	diplopia improved. She was discharged from the hospital. JC virus DNA in the CSF was negative. MRI findings revealed mild improvement.

Laboratory test value

	Before initiation of admin.	Approximately 8 years after admin. (day of hospitalization)	Day of discontinuation (day of rehospitalization)	8 weeks after discontinuation	16 weeks after discontinuation
Revised Hasegawa dementia scale (score)	—	28	16	28	—
Mini-Mental State (score)	—	30	—	—	—
WBC counts (cells/μL)	—	—	5 400	—	—
Lymphocyte (%)	—	—	4.0	—	—
Human immunodeficiency virus (HIV) antibody	—	—	negative	—	—
Blood glucose (mg/dL)	—	—	143	—	—
WBC counts in CSF (cells/μL)	—	—	23	—	10
Protein in CSF (mg/dL)	—	—	199	—	—
Glucose in CSF (mg/dL)	—	—	22	—	—
JC virus DNA in CSF (copies/mL)	—	—	479	—	0

Suspected concomitant drug: Infliximab
Concomitant drug: Prednisolone

4
Revision of Precautions (No.336)

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, 2022.

1 Antipyretics, analgesics and anti-inflammatory agents

Loxoprofen sodium hydrate (oral dosage form) (prescription drug)

Brand name	Loxonin Tablets 60 mg, Loxonin Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis

2 Agents affecting metabolism, n.e.c. (not elsewhere classified), antimetabolic agents

Methotrexate

Brand name	[1] Rheumatrex Capsules 2 mg (Pfizer Japan Inc.), and the others, [2] Methotrexate Tablets 2.5 mg (Pfizer Japan Inc.), [3] Methotrexate Injection 200 mg, 1000 mg (Pfizer Japan Inc.), [4] Methotrexate Parenteral 5 mg (Pfizer Japan Inc.), [5] Methotrexate Parenteral 50 mg (Pfizer Japan Inc.)
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leukoencephalopathy (PML) may occur. Patients should be carefully monitored during and after the treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia or quadriplegia), dyslalia, or speech loss are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Progressive multifocal leukoencephalopathy (PML) Patients should be carefully monitored during and after the treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, paralytic symptoms (hemiplegia or quadriplegia), dyslalia, or speech loss are observed, diagnostic imaging through MRI and cerebrospinal fluid test should be performed, administration should be discontinued, and appropriate measures should be taken.

3 Other antitumor agents

Ipilimumab (genetical recombination)

Brand name	Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	Uveitis may occur. Whether ocular abnormalities have occurred should be examined periodically. In addition, patients should be instructed to immediately seek medical attention if any ocular abnormalities are observed.
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Uveitis

4 Other antitumor agents

Nivolumab (genetical recombination)

Brand name	Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Uveitis may occur. Whether ocular abnormalities have occurred should be examined periodically. In addition, patients should be instructed to immediately seek medical attention if any ocular abnormalities are observed.
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Uveitis

5 Other antitumor agents

Pembrolizumab (genetical recombination)

Brand name	Keytruda Injection 100 mg (MSD K.K.)
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Uveitis

6 Other chemotherapeutics

Itraconazole (tablets, capsules)

Brand name	Itrizole Capsules 50 (Janssen Pharmaceutical K.K.), and the others
[Under old instructions]	
Important Precautions (newly added)	Hypokalaemia may occur. Periodic blood electrolyte test should be performed.
Adverse Reactions	Hypokalaemia:
Clinically Significant Adverse Reactions (newly added)	Hypokalaemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	Hypokalaemia may occur. Periodic blood electrolyte test should be performed.

<Common to all indications> **(newly added)** **11. ADVERSE REACTIONS** **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Hypokalaemia

7 Other chemotherapeutics

Itraconazole (oral solution)

Brand name	Itrizole Oral Solution 1% (Janssen Pharmaceutical K.K.), and the others
[Under old instructions]	
Important Precautions (newly added)	Hypokalaemia may occur. Periodic blood electrolyte test should be performed.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Hypokalaemia: Hypokalaemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Hypokalaemia may occur. Periodic blood electrolyte test should be performed.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Hypokalaemia

8 Other chemotherapeutics

Itraconazole (injections)

Brand name	Itrizole Injection 1% [200 mg] (Janssen Pharmaceutical K.K.)
[Under old instructions]	
Important Precautions (newly added)	Hypokalaemia may occur. Periodic blood electrolyte test should be performed.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Hypokalaemia: Hypokalaemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

9 Antipyretics and analgesics

Preparations containing loxoprofen sodium hydrate (oral dosage form) (OTC drugs)

Brand name	Loxonin S, Loxonin S Quick, Loxonin S plus, Loxonin S Premium (Daiichi Sankyo Healthcare Co., Ltd.), and the other OTC drugs
Consultation	If the following symptoms are observed after taking this drug, these may be adverse reactions. In such a case, the use of this drug should be immediately discontinued, and a physician, dentist or pharmacist should be consulted with this document. The following serious symptoms may occur rarely. In such a case, medical attention should be sought immediately.

Name of symptoms	Symptoms

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, erythema multiforme, acute generalized exanthematous pustulosis	Some symptoms, such as hyperthermia, ocular hyperaemia, eye discharge, sore lips, pharynx pain, widespread skin rash/redness, blisters on reddened skin, small pimples (small pustules) on reddened skin, general malaise, and anorexia, may persist or suddenly worsen.

10 Agents for hyperlipidemias

Pemafibrate

Brand name	Parmodia Tab. 0.1 mg (Kowa Company, Ltd.)
[Under old instructions]	
Contraindications	(deleted)
Precautions concerning Dosage and Administration	Rhabdomyolysis accompanied by rapid deterioration of renal function may occur. When using this drug, patients should be monitored for the renal function. If the eGFR is less than 30 mL/min/1.73 m^2, administration of this drug should be initiated at a low dose or the dosing interval should be prolonged. In addition, the maximum daily dose should be limited to 0.2 mg.
Careful Administration	Patients with renal impairment whose eGFR is less than 30 mL/min/1.73 m^2 [Rhabdomyolysis may occur.]
Important Precautions	In patients with renal impairment, rhabdomyolysis accompanied by rapid deterioration of renal function may occur. When using this drug, patients should be monitored for the renal function. If the eGFR is less than 30 mL/min/1.73 m^2, appropriate measures should be taken such as dose reduction or prolongation of the dosing interval of this drug.

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, 2022)
◎: Products for which EPPV was initiated after September 1, 2022

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Fesoterodine fumarate[*1] Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	September 26, 2022
◎	Aflibercept (genetical recombination) [*2] Eylea solution for IVT inj. 40 mg/mL	Bayer Yakuhin Ltd.	September 26, 2022
◎	Upadacitinib hydrate[*3] [1] Rinvoq Tablets 7.5 mg, [2] 15 mg, [3] 30 mg, [4] 45 mg	AbbVie GK	September 26, 2022
◎	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) [*4] Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	September 20, 2022
◎	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) [*5] Comirnaty RTU intramuscular injection	Pfizer Japan Inc.	September 14, 2022
◎	Ethyl icosapentate Epadel EM Capsules 2 g	Mochida Pharmaceuticals Co. Ltd.	September 12, 2022
◎	Sutimlimab (genetical recombination) Enjaymo for I.V. infusion 1.1 g	Sanofi K.K.	September 8, 2022
	Tixagevimab (genetical recombination) and cilgavimab (genetical recombination) Evusheld Intramuscular Injection Set	AstraZeneca K.K.	August 31, 2022
	Pimitespib Jeselhy tablets 40 mg	TAIHO Pharmaceutical Co., Ltd.	August 30, 2022
	Icatibant acetate Firazyr subcutaneous injection 30 mg syringes	Takeda Pharmaceutical Company Limited.	August 24, 2022
	Ravulizumab (genetical recombination) [*6] Ultomiris for Intravenous Infusion 300 mg, 300 mg/3 mL, Ultomiris for Intravenous Infusion 1100 mg/11 mL	Alexion Pharma Godo Kaisha	August 24, 2022

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Landiolol hydrochloride[*7] Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	August 24, 2022
Darinaparsin Darvias Injection 135 mg	Solasia Pharma K.K.	August 22, 2022
Vestronidase alfa (genetical recombination) Mepsevii Intravenous Infusion 10 mg	Amicus Therapeutics, Inc.	August 22, 2022
Vosoritide (genetical recombination) Voxzogo for Subcutaneous Injection 0.4 mg, 0.56 mg, 1.2 mg	BioMarin Pharmaceutical Japan KK.	August 19, 2022
Nemolizumab (genetical recombination) Mitchga 60 mg Syringes	Maruho Co., Ltd.	August 8, 2022
Freeze-dried Smallpox Vaccine Prepared in Cell Culture[*8] Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB”	KM Biologics Co., Ltd.	August 2, 2022
[1] [2] Cabotegravir, [3] Cabotegravir sodium, [4] [5] Rilpivirine [1] Vocabria Aqueous Suspension for IM Injection 400 mg, [2] Vocabria Aqueous Suspension for IM Injection 600 mg, [3] Vocabria Tablets 30 mg, [4] Rekambys Aqueous Suspension for IM Injection 600 mg, [5] Rekambys Aqueous Suspension for IM Injection 900 mg	[1] [2] [3] ViiV Healthcare K.K. [4] [5] Janssen Pharmaceutical K.K.	June 27, 2022
Emicizumab (genetical recombination)[*9] Hemlibra for Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	June 20, 2022
Daptomycin Cubicin IV 350 mg	MSD K.K.	June 20, 2022
Brolucizumab (genetical recombination) [*10] Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	June 20, 2022
Rituximab (genetical recombination) [*11] Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	June 20, 2022
Lasmiditan succinate Reyvow tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	June 8, 2022
Avacopan Tavneos Capsules 10 mg	Kissei Pharmaceutical Co., Ltd.	June 7, 2022
Olipudase alfa (genetical recombination) Xenpozyme for I.V. Infusion 20 mg	Sanofi K.K.	June 3, 2022
Finerenone Kerendia tablets 10 mg, 20 mg	Bayer Yakuhin Ltd.	June 2, 2022
Valbenazine tosilate Dysval Capsules 40 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2022
Difamilast Moizerto ointment 0.3%, 1%	Otsuka Pharmaceutical Co., Ltd.	June 1, 2022

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Carotegrast methyl Carogra Tablets 120 mg	EA Pharma Co., Ltd.	May 30, 2022
	Fosnetupitant chloride hydrochloride Arokaris I.V. infusion 235 mg	TAIHO Pharmaceutical Co., Ltd.	May 30, 2022
	Tolvaptan sodium phosphate Samtasu for I.V. infusion 8 mg, 16 mg	Otsuka Pharmaceutical Co., Ltd.	May 30, 2022
	Lanadelumab (genetical recombination) Takhzyro subcutaneous injection 300 mg syringes	Takeda Pharmaceutical Company Limited.	May 30, 2022
	Metronidazole*12 Rozex Gel 0.75%	Maruho Co., Ltd.	May 26, 2022
	Asciminib hydrochloride Scemblix tablets 20 mg, 40 mg	Novartis Pharma K.K.	May 25, 2022
	Faricimab (genetical recombination) Vabysmo solution for Intravitreal Injection 120 mg/mL	Chugai Pharmaceutical Co., Ltd.	May 25, 2022
	Andexanet alfa (genetical recombination) Ondexxya for Intravenous Injection 200 mg	Alexion Pharma Godo Kaisha	May 25, 2022
	Glycopyrronium tosilate hydrate Rapifort Wipes 2.5%	Maruho Co., Ltd.	May 23, 2022
	Recombinant COVID-19 (SARS-CoV-2) vaccine Nuvaxovid Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 10, 2022
	Efgartigimod Alfa (genetical recombination) Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	May 9, 2022
	Somatrogon (genetical recombination) Ngenla Inj. 24 mg Pens, 60 mg Pens	Pfizer Japan Inc.	April 27, 2022
	Gefapixant citrate Lyfnua Tablets 45 mg	MSD K.K.	April 21, 2022
	Sotorasib Lumakras Tablets 120 mg	Amgen K.K.	April 20, 2022
	Clazosentan sodium Pivlaz I.V. Infusion liquid 150 mg	Idorsia Pharmaceuticals Japan Ltd.	April 20, 2022
	Bimekizumab (genetical recombination) Bimzelx Syringe for S.C injection 160 mg, Bimzelx Autoinjector for S.C injection 160 mg	UCB Japan Co. Ltd.	April 20, 2022

*1 A drug with a new additional pediatric dosage indicated for urinary management in patients with neurogenic bladder

*2 Retinopathy of prematurity

*3 [1] [2] [3] Remission induction and maintenance therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments), [4] remission induction therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments)

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

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

*6 Treatment of generalized myasthenia gravis (only for patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or plasmapheresis)

*7 A drug with a new additional pediatric dosage indicated for the treatment of tachyarrhythmia (supraventricular tachycardia, atrial fibrillation and atrial flutter) in patients with low cardiac function

*8 Monkeypox
*9 Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with acquired hemophilia A
*10 Diabetic macular oedema
*11 Prevention of recurrence of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
*12 Rosacea