Pharmaceuticals and Medical Devices Safety Information

No. 387 November 2021

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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 (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://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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Pharmaceuticals and Medical Devices Safety Information

No. 387 November 2021

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

[Outline of Information]

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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, it is mandatory for such providers to 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.

Abbreviations

ADR	Adverse drug reaction
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HPV	Human papilloma virus
HSB	Health Service Bureau
MACE	Major Adverse Cardiovascular Events
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
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SD	Safety Division
SYB	Sports and Youth Bureau
V-A ECMO	Veno-arterial extracorporeal membrane oxygenation

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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) (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 suffered 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 26 159 cases have been granted relief benefits since its establishment in 1980 until the end of fiscal year (FY) 2020.

2. Awareness of the Relief System for Adverse Drug Reactions

Awareness of the Relief System among the general public in FY 2020 was 25.5% in total according to the FY 2020 survey: 7.6% answered that they “were aware” of the Relief System and 17.9% 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: 60.3% answered that they “were aware” of the Relief System and 23.5% answered that they “have heard about” the Relief System. By occupational category, awareness was 94.0% among physicians, 99.0% among pharmacists, 62.0% among nurses, and 79.7% among dentists. Among the healthcare professionals who were aware of the Relief System, the proportion of them who had been involved in a filing procedure was 7.0% overall: 10.1% among physicians, 8.5% among pharmacists, 2.8% among nurses, and 2.7% among dentists [Note 1)].

Furthermore, in all application forms related to relief benefits, the 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 2020 results showed “Physician” in 458 answers (30.6%), “Others” (the Internet) in 275 answers (18.3%), “Pharmacist” in 163 answers (10.9%) and “Newspaper/TV, etc.” in 156 answers (10.4%) in descending order (multiple answers acceptable) [Note 2)].

In June 2014, a field for information on the Relief System was newly added to the form of the Pharmaceuticals and Medical Devices Safety Information Report, the form for healthcare professionals to report ADRs. 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 ADRs are requested to consider

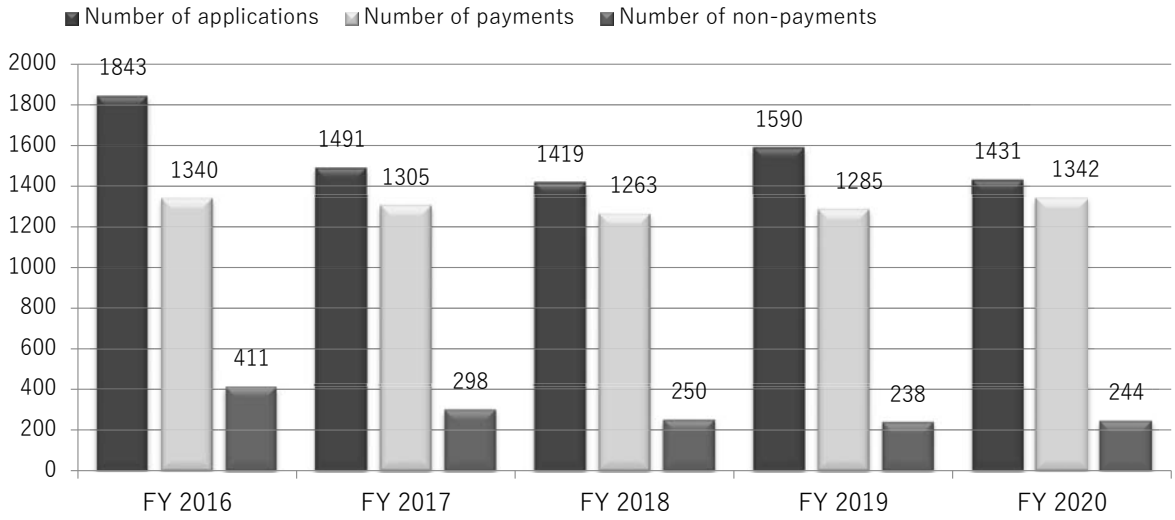
introducing the Relief System to the patient. Healthcare professionals should provide information on the Relief System to people who have suffered from adverse health effects associated with adverse reactions to drugs or regenerative medical products so that they can benefit from the Relief System, and should also cooperate with the preparation of medical certificates, etc. when people suffering from adverse health effects file an application for compensation.

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

The annual numbers of applications and payments in the Relief System between FY 2016 and FY 2020 are shown in Figure 1. In FY2020, the number of applications was 1 431, the number of payments was 1 342, and the number of non-payments was 244. The ratios between payment and non-payment and details of reasons for non-payments from FY 2016 to FY 2020 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 6 months or less, 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 2020 was 55.0% affected by measures taken to prevent the spread of COVID-19.

Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2016 to FY 2020)

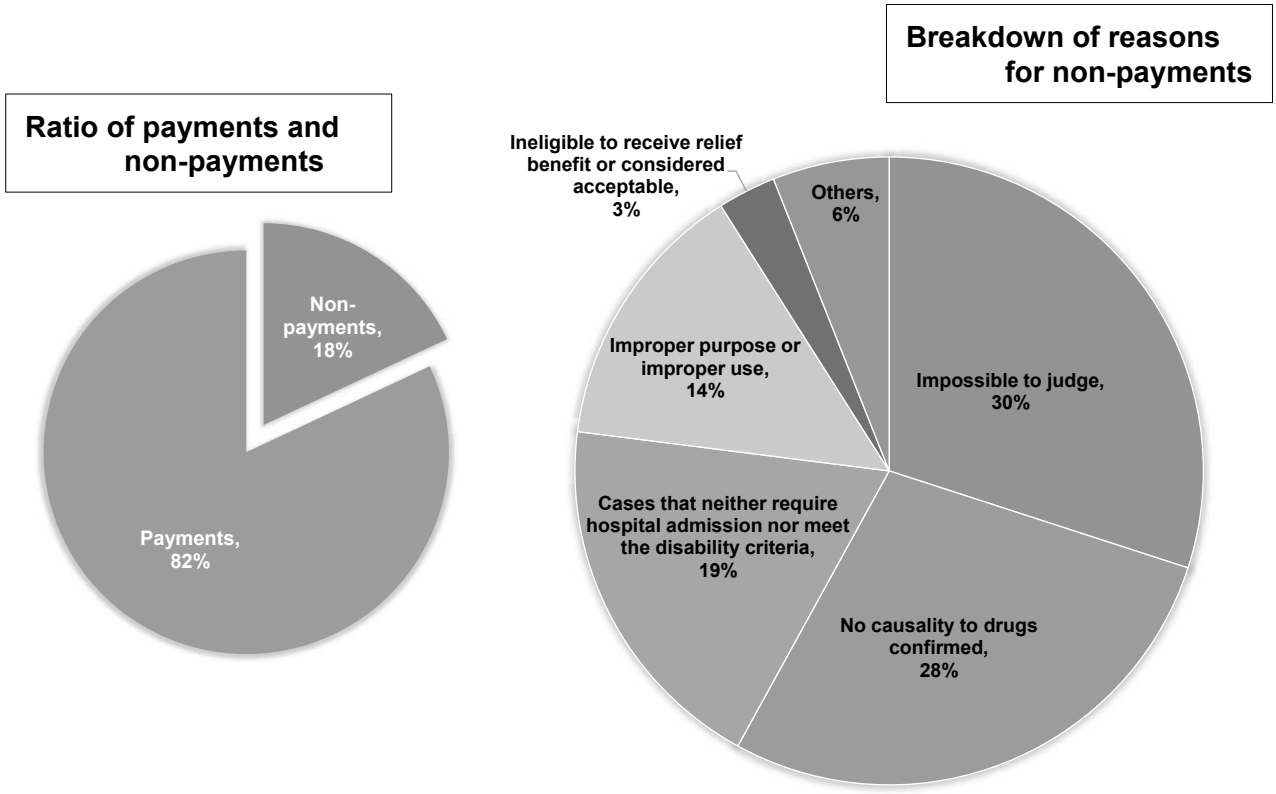


(Graph description)

*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 judgement to provide relief benefits, the number of claims does not correspond to the total number of relief benefits provided/claim withdrawals within the same fiscal year.

Figure 2 Ratio of payments and non-payments and breakdown of reasons for non-payments between FY 2016 and FY 2020



4. 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.

Please refer to the details of the Relief System noted on the PMDA website (https://www.pmda.go.jp/english/relief-services/0002.html).

[Types and amounts of relief benefits (as of April 1, 2021)]
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 (35 000 to 37 000 yen per month)
• Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs.
Disability Pension (Grade 1: 2 809 200 yen per year, Grade 2: 2 247 600 yen per year)
• Benefits are provided to compensate for living costs, etc., of patients aged 18 years or older, who suffer from a certain degree of disability caused by ADRs.
Pension for Raising Children with disabilities (Grade 1: 878 400 yen per year, Grade 2: 703 200 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 (2 457 600 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 (7 372 800 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.

[Cases of relief benefit payments]
<Case 1> A case of myelitis due to an influenza vaccine, for which medical expenses and medical allowance benefits were provided

A man in his 20s developed myelitis following vaccination of Influenza HA vaccine "KMB" and received inpatient treatment. Medical expenses and medical allowance benefits were provided.

<Case 2> A case of necrolysis epidermal toxic (Lyell syndrome) due to acetaminophen tablets, for which medical expenses, medical allowance, bereaved family benefits, and funeral expenses benefits were provided

A man in his 60s developed toxic epidermal necrolysis (Lyell syndrome) after using Calonal tablets and Acetaminophen Tab."Maruishi" (acetaminophen) and received inpatient treatment. He died from pneumonia secondary to toxic epidermal necrolysis (Lyell syndrome). Medical allowance, bereaved family pension, and funeral expenses benefits were provided.

<Case 3> A case of anaphylactic shock and secondary hypoxic encephalopathy due to pentazocine injection, hydroxyzine injection, sulbactam sodium/cefoperazone sodium for intravenous injection, which led to a disability status, and disability pension benefits were provided

A woman in her 80s developed anaphylactic shock and higher brain dysfunction caused by secondary hypoxic encephalopathy following use of Sosegon Injection (pentazocine), Atarax-P Parenteral Solution (hydroxyzine) and Cefocef for intravenous injection (sulbactam sodium/cefoperazone sodium). Medical expenses, medical allowance benefits and disability pension benefits were provided.

<Case 4> A case of urinary retention and secondary urinary tract infection due to an OTC drug. Medical expenses and medical allowance benefits were provided.

A man in his 80s experienced urinary retention and secondary urinary tract infection following use of Pabron Gold A <Granules>, Benza Ace A Tablets and received inpatient treatment. Medical expenses and medical allowance were provided.

5. Cases in which the proper use of drugs could not be confirmed

Of the 1 441[Note 4)] non-payment cases from FY 2016 to FY 2020, the reason for non-payment in approximately 14% 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. 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 2016 to FY 2020)

Name of causative drug	FY 2016	FY 2017	FY 2018	FY 2019	FY 2020	Total (cases)
Lamotrigine	24	9	12	15	8	68
Thiamazole	3	1	3	2	4	13
Lithium carbonate	8	0	1	3	0	12
Methotrexate	0	1	1	4	5	11
Others	19	17	27	22	18	103
Total (cases)	54	28	44	46	35	207

(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 paper package insert or electronic package insert (hereinafter referred to as “package insert, etc.”) 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 initiating administration)

A man in his 20s used Lamotrigine Tablets 25 mg “AMEL” for mood disorder of bipolar disorder with drugs other than those inducing glucuronidation. Lamotrigine was started from a daily dose of 75 mg with the first dose. Therefore, this drug use was not considered proper.

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

A woman in her 10s used Lamictal Tablets (lamotrigine) for epilepsy. As monotherapy the drug was started from a daily dose of 25 mg, but the dose was increased to 50 mg after 6 days when it should have been 25 mg once daily for the first 2 weeks. Therefore, this drug use was not considered proper.

<u>Improper use of lamotrigine</u>

It has been demonstrated in a clinical study conducted in Japan that the incidence of skin disorders is high when lamotrigine is administered at a dose exceeding the approved dosage and administration, and there has been an alert since the approval of Lamictal Tablets in October 2008 to adhere to the specified dosage and administration. However, severe skin disorders have 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 has been no end to 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 package insert, etc. of the original drug (Lamictal) are shown below as an example. Please make sure to read the latest package inserts, etc. carefully before use, including other dosage and administration.

Package insert, etc. of Lamictal Tablets (revised in April 2021)

Concomitant drugs with lamotrigine	Concomitant medication			(1) Lamotrigine monotherapy
	(2) With sodium valproate	(3) Without sodium valproate[Note1)]		
		(3)-i) With drugs that induce glucuronidation of lamotrigine[Note2)]	(3)-ii) With drugs other than (3)-i)[Note3)]	
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

(Note 1) In combination therapy with drugs whose effects on the glucuronidation of lamotrigine are not known, the dosage and administration for concomitant use with sodium valproate should be followed.

(Note 2) Drugs that induce glucuronidation of lamotrigine: Phenytoin, carbamazepine, phenobarbital, primidone, rifampicin, lopinavir/ritonavir combination agents

(Note 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 package inserts, etc. 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 package insert once again.

<Case 1> A case of drug-induced liver injury due to iguratimod

A woman in her 70s. Careram Tablets (igratimod) was started at 25 mg/day, and the dose was increased to 50 mg/day after 17 days. In addition, no blood tests including liver function tests were performed for approximately 30 days following the blood tests 2 weeks after the start of iguratimod until hepatic impairment was observed. Thus, the case was not considered as proper use.

Description in the package insert, etc. (revised October 2019) of Careram Tablets (partial excerpt)

DOSAGE AND ADMINISTRATION

The usual adult dosage is 25 mg of iguratimod taken orally. Once daily after breakfast for at least 4 weeks, after which the dosage should be increased to 25 mg per dose taken twice daily (after breakfast and dinner).

IMPORTANT PRECAUTIONS

Liver function tests should be performed prior to administration of this drug. In addition, patients should be carefully monitored for clinical symptoms during the administration. Liver function tests should be performed periodically, such as once every 2 weeks for the first 2 months and once a month thereafter.

<Case 2> A case of hypercalcemia due to eldecalcitol

A woman in her 70s. Although a decrease in eGFR and a trend toward higher creatinine levels were observed, the patient, who was elderly and had a history of chronic kidney disease and elevated serum calcium levels, was continuously administered Edirol Capsules (eldecalcitol) for approximately 2 years without measuring serum calcium levels until she was diagnosed with acute renal failure due to hypercalcemia. Thus, the case was not considered as proper use.

Description in the package insert, etc. (revised June 2020) of Edirol Capsules (partial excerpt)

PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

Serum calcium levels should be measured periodically. If hypercalcemia occurs, the drug should be withdrawn immediately. After withdrawal, the drug should be resumed with 0.5 μg once daily after the serum calcium level recovers to the normal range. (The rest is omitted.)

IMPORTANT PRECAUTIONS

During treatment with Edirol Capsules, serum calcium should be measured periodically (approximately once every 3 to 6 months). When any abnormalities are observed, the drug should be withdrawn immediately and appropriate measures should be taken. Particular caution should be exercised through frequent measurement of serum calcium in the early phase of treatment for example in patients with renal impairment, malignant tumor, primary hyperparathyroidism, etc. who may develop hypercalcaemia.

(3) Cases of use in patients falling under the CONTRAINDICATIONS

There are also cases where the drug was used (continued) 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 of continuous use of methotrexate in a patient with chronic liver disease

A woman in her 70s. Approximately 5 and a half years after the start of Rheumatrex Capsules (methotrexate) for rheumatoid arthritis, the patient was diagnosed with non-B non-C hepatic cirrhosis. Even after that, methotrexate was continuously administered for approximately 2 years despite the appearance of signs of hepatic failure and ascites retention. Thus, the case was not approved as proper use.

Description in the package insert, etc. (partial excerpt) of Rheumatrex Capsules (revised March 2019)

CONTRAINDICATIONS (This drug should not be administered to the following patients.)
Patients with chronic liver diseases [Adverse reactions may be more severe.]
Patients with pleural effusion, ascites, etc. [Toxicity of methotrexate may be more severe due to prolonged retention in pleural effusion, ascites, etc.]
Clinically Significant Adverse Reactions
Fulminant hepatitis, hepatic failure (both with frequency unknown): Serious hepatic disorder (including those caused by hepatitis B or C virus) such as fulminant hepatitis, hepatic failure, necrosis and fibrosis of hepatic tissue, or hepatic cirrhosis may occur. Patients should be carefully monitored through liver function tests every 4 weeks for example. If any abnormalities are observed, appropriate measures should be taken such as discontinuation of administration.

(4) 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 or dosing conditions, and doses to allow patients to manage their drugs appropriately.

<Case 1> A case of acute generalised exanthematous pustulosis (AGEP) due to azithromycin, fexofenadine hydrochloride/pseudoephedrine hydrochloride and Shin-Dickinin granules

A woman in her 50s. The patient was taking Zithromac Tablets (azithromycin), Dellegra Combination Tablets (fexofenadine hydrochloride/pseudoephedrine hydrochloride) and Shin-Dickinin granules. Of these, the patient took the residual Zithromac Tablets (azithromycin) that were previously prescribed by her physician at her own discretion. Thus, the case was not considered proper.

(5) Cases where patients were administered the drugs to which they had a history of adverse reactions

There are cases where patients were prescribed drugs to which they had a history of adverse reactions by physicians who knew the history and the uses were 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 of hyponatraemia due to indapamide

A woman in her 80s. Despite her history of hyponatraemia due to Natrix Tablets (indapamide), the tablets were prescribed without measuring the patient's blood sodium level and hyponatraemia developed. This drug use was not considered proper.

Healthcare professionals should reconfirm the descriptions in the package inserts, etc. 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 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 package inserts, etc.)
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 Comments

Healthcare professionals are encouraged to fully check the necessary alerts in the package inserts, etc. 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.

If they become aware of ADRs, etc. or if they are consulted by their patients about ADRs, healthcare professionals should provide information on the Relief System to the patients or their caregivers if the adverse health effects are possibly eligible to receive 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 2020 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 2021 Relief Service Committee (Pharmaceuticals and Medical Devices Agency)
https://www.pmda.go.jp/about-pmda/advisory-council-information/relief-services/0053.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) If 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 2021, 317 of the total 525 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 relief benefits.
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
Number of claims	2 cases	10 cases	7 cases	25 cases	39 cases	152 cases
Number of Payments	0	5 cases	9 cases	8 cases	4 cases	75 cases
Fiscal Year	2016	2017	2018	2019	2020	Total
Number of claims	334 cases	141 cases	86 cases	58 cases	34 cases	888 cases
Number of Payments	314 cases	223 cases	111 cases	75 cases	49 cases	873 cases

(Source: PMDA Annual Report FY 2020)
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 patient may submit multiple applications 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 Sports and the Director of the 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 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/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

Acute coronary syndrome accompanying allergic reaction (Kounis Syndrome)

1. Introduction

The MHLW on October 12, 2021 issued a notification instructing the addition of a cautionary statement regarding “acute coronary syndrome accompanying allergic reaction” (Kounis syndrome) to the precautions of the package insert for cefoperazone sodium/sulbactam sodium (hereinafter referred to as “this drug”). The decision was in response to the cases of Kounis syndrome that were reported in Japan in which a causal relationship between the drug and event was reasonably possible. Since the definition of Kounis syndrome could not be confirmed in Japanese or overseas guidelines and other relevant documents as of October 2021 and it was considered that the syndrome was not highly recognized in Japan, the addition of “acute coronary syndrome accompanying allergic reaction” to the precautions was decided.

Please refer to 3. Important Safety Information and 4. Revision of Precautions (No. 327) for the details of the revision and clinical courses of the cases.

2. Kounis syndrome

(1). Diseases concept

Kounis syndrome is, according to the literature, a disease in which various pathological conditions related to acute coronary syndrome are caused by different mediators released from mast cells due to allergic reactions [i, ii]. There are 3 types of Kounis syndrome: Type I which causes spasm in the coronary arteries with no significant preexisting stenosis, type II which causes acute coronary syndrome secondary to rupture of the preexisting coronary plaque, and Type III which causes in-stent thrombosis in patients with coronary artery stent implantation.

(2). Epidemiology

Only a limited number of cases of Kounis syndrome have been reported in the literature. The poor awareness of the syndrome in clinical practice is considered to be a reason for the limited number. It is assumed that there are cases of anaphylaxis and acute coronary syndrome that were not diagnosed as Kounis syndrome, and the actual number of patients with Kounis syndrome may be higher than the number of reported cases [i, iii, iv].

(3). Causes

It is believed that Kounis syndrome potentially occurs with anything that may cause an allergic reaction. Drugs that may cause an allergic reaction and therefore potentially cause Kounis syndrome include antibiotics, contrast media, antiplatelet agents, and anticancer drugs. In addition to drugs, a wide range of substances and circumstances are considered to potentially cause the syndrome such as food allergies, metal allergies, insect and fish stings, and bites [v].

(4). Diagnosis

There are no established diagnostic criteria for Kounis syndrome. As of October 2021, no descriptions of Kounis syndrome are identified in Japanese and overseas guidelines. The possibility of Kounis syndrome is to be considered for cases diagnosed with coronary spastic angina or acute myocardial infarction associated with allergic reaction based on clinical symptoms, blood tests, and imaging assessment. A possibility of being complicated with acute coronary syndrome should be assumed for cases presenting with allergic reactions including anaphylaxis as well as a possibility of being caused by allergic reaction for cases of acute coronary syndrome.

(5). Treatment

For Kounis syndrome, allergic reaction and acute coronary syndrome should be treated concurrently. Depending on the treatment regimen, treatment for allergic reaction may aggravate acute coronary syndrome, or treatment for acute coronary syndrome may aggravate allergic reaction, so care must be taken in selecting drugs [vi].

3. Request for cooperation

Kounis syndrome is considered to be an event that potentially occurs with any drugs that may cause an allergic reaction. Medical professionals who encounter a case suggestive of Kounis syndrome caused by a drug (cases of acute coronary syndrome that occurs accompanying allergic reaction) are requested to cooperate through reporting to the PMDA pursuant to the Drugs and Medical Devices Safety Information Reporting System or informing the marketing authorization holder (MAH) of the drug of such cases. The MHLW and PMDA will continue to closely monitor for cases in which Kounis syndrome due to drugs other than this drug is suspected as well and to consider the necessity of safety measures.

[References]

- Revisions of Precautions (PSEHB/PSD 1012 No.1 dated October 12, 2021)
  https://www.mhlw.go.jp/content/11120000/000842056.pdf (only in Japanese)
  English translation by PMDA (cefoperazone sodium/sulbactam sodium)
  https://www.pmda.go.jp/files/000243227.pdf
- Adverse Reactions, Infections, Malfunctions Report pursuant to the Pharmaceuticals and Medical Devices Act (intended for healthcare professionals)
  https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html (only in Japanese)

<Literature>

[i] Kounis NG, et al. : Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract. 45: 121‐8(1991).
[ii] Kounis NG. : Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med. 54: 1545‐59(2016).
[iii] Wu H, et al. : Kounis Syndrome Induced by Anisodamine: A Case Report. Int J Gen Med. 13: 1523-7(2020)
[iv] Li J, et al. : Acute coronary syndrome secondary to allergic coronary vasospasm (Kounis Syndrome): a case series, follow-up and literature review. BMC Cardiovasc Disord. 18: 42(2018).
[v] Ng BH, et al. : Kounis syndrome following solenopsis (fire ant) bite. Med J Malaysia. 74: 344-6(2019).
[vi] Fassio F, et al. : Kounis syndrome: A concise review with focus on management. Eur J Intern Med. 30: 7-10(2016).

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated October 12, 2021, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Cefoperazone sodium/sulbactam sodium

Branded name (name of company)	a. Sulperazon for Intravenous Use 0.5 g, b. Sulperazon for Intravenous Use 1 g, c. Sulperazon Kit for Intravenous Use 1 g (Pfizer Japan Inc.), and the others
Therapeutic category	Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria
Indications	<Applicable microorganisms> Cefoperazone sodium/sulbactam sodium-susceptible strains of genus *Staphylococcus*, *Escherichia coli*, genus *Citrobacter*, genus *Klebsiella*, genus *Enterobacter*, genus *Serratia*, genus *Proteus*, genus *Providencia rettgeri*, *Morganella morganii*, *Haemophilus influenza*, *Pseudomonas aeruginosa*, *genus Acinetobacter*, genus *Bacteroides*, and genus *Prevotella* species <Applicable conditions> Sepsis, infective endocarditis, secondary infections following trauma, thermal burn, and surgical wound, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, lung abscess, pyothorax, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, peritonitis, intra-abdominal abscess, cholecystitis, cholangitis, liver abscess, bartholinitis, intrauterine infection, uterine adnexitis, parametritis

PRECAUTIONS (revised language is underlined)

[Under old instructions]	
Important Precautions	Since no methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction associated with this drug with reasonable certainty, the following measures should be taken.
Adverse Reactions **Clinically Significant Adverse Reactions**	Shock, anaphylaxis (dyspnoea, etc.)<u>, acute coronary syndrome accompanying allergic reaction</u>: Shock, anaphylaxis (dyspnoea, etc.)<u>, or acute coronary syndrome accompanying allergic reaction</u> may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	Since no methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction associated with this drug with reasonable certainty, the following measures should be taken.
11. ADVERSE REACTIONS	Shock, anaphylaxis (dyspnoea, etc.), acute coronary syndrome accompanying allergic reaction

11.1 Clinically Significant Adverse Reactions 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 (April 2018 to March 2021)

Cases involving acute coronary syndrome accompanying allergic reaction: 2 (1 patient mortality)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately a: 7 270, b: 61 752, c: 66 539

Japanese market launch: a,b: June 1986, c: July 1997

Case

No.	Patient		Daily dose/ administration duration	Adverse Reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Male 70s	Cholangitis (bile duct cancer)	No data/ for 1 day ↓ Discontinued	**Kounis syndrome Type 1** Patient background: Surgery was performed for bile duct cancer 3 year ago, followed by several hospital admissions for postoperative recurrent cholangitis, which was treated in part with cefoperazone sodium/sulbactam sodium. Recurrence of cholangitis was noted during chemotherapy for bile duct cancer. Treatment with cefoperazone sodium/sulbactam sodium was initiated again. On Day 1 of administration (Day of discontinuation), the patient complained of rash and pruritus immediately following administration of cefoperazone sodium/sulbactam sodium and then had cardio-respiratory arrest. Cardiopulmonary resuscitation and electrical cardioversion were repeated but the patient did not respond. Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) was established and extracorporeal cardiopulmonary resuscitation (ECPR) was performed. ST elevation was noted in the aVR on 12-lead ECG without return of spontaneous circulation. Emergency coronary angiography (CAG) was undertaken. Diffuse vascular spasm and delayed enhancement in the 3 major coronary arteries were identified. The arteries were recanalized by administering a vasodilator intracoronarily. Spontaneous circulation returned after an intra-aortic balloon pump (IABP) was inserted. The patient died of progressing multi-organ failure 1 day after discontinuation of cefoperazone sodium/sulbactam sodium despite the assisted circulation by V-A ECMO and IABP.

	Day 1 of administration
Peak CK (U/L)	19 378
Peak CK-MB (U/L)	1 041

Suspected concomitant drugs: No data
Concomitant drugs: No data

4
Revision of Precautions (No.327)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated September 21, October 12, 2021.

1 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Branded name	Comirnaty intramuscular injection (Pfizer Japan Inc.)
[Under New instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Number of doses This vaccine has had its effectiveness confirmed as a two-dose series. In principle, completion of both doses of the series with this vaccine should be ensured and no other vaccines with the same indications should be used in this vaccination series.

2 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Branded name	COVID-19 Vaccine Moderna Intramuscular Injection (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Number of doses This vaccine has had its effectiveness confirmed as a two-dose series. In principle, completion of both doses of the series with this vaccine should be ensured and no other SARS-CoV-2 vaccines should be used in this vaccination series.

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

Branded name	Vaxzevria Intramuscular Injection (AstraZeneca K.K.)
[Under New instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	This vaccine has had its effectiveness confirmed as a two-dose series. In principle, completion of both doses of the series with this vaccine should be ensured and no other vaccines with the same indications should be used in this vaccination series.

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

Branded name	Xeljanz Tablets 5 mg (Pfizer Japan Inc.)
[Under New instructions]	
1. WARNINGS	New onset or worsening of serious infection by tuberculosis, pneumonia, sepsis, or virus infection as well as onset of malignancy has been reported following administration of this drug. Including the fact that this drug is not an agent to completely cure a disease, such information should be fully made known to patients and their understanding should be ensured before this drug is administered. In addition, this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. Serious adverse reactions may also occur and take a fatal course following administration of this drug. This drug should be used in the

	healthcare facilities and by the physicians that are highly capable of responding to emergencies, and patients should be warned to contact their physicians immediately if such adverse reactions occur following administration of this drug.
5. PRECAUTIONS CONCERNING INDICATIONS	<Common to all indications> When administration of this drug is considered in patients with risk factors of cardiovascular events, alternative treatments should be considered first, since cardiovascular events such as myocardial infarction or venous thromboembolism may occur.
8. IMPORTANT PRECAUTIONS	Onset of malignancy such as malignant lymphoma and solid tumor has been reported. Also there has been a report that a trend toward a higher incidence of malignancy was observed with this drug compared with TNF inhibitors in an overseas clinical study. Caution should be exercised for the onset of malignancy.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.**	Patients with risk factors of cardiovascular events Alternative treatments should be considered first. In particular, the necessity of administration at 10 mg twice daily should be determined with caution. When this drug is administered, the onset of signs and symptoms of cardiovascular events such as myocardial infarction and venous thromboembolism should be closely monitored. In an overseas clinical study in patients with rheumatoid arthritis who had risk factors of cardiovascular events (such as smoking, hypertension, diabetes mellitus, and a history of coronary artery disease), a trend toward a higher incidence of cardiovascular events such as myocardial infarction was observed in the groups that received this drug compared with the TNF inhibitors group. A trend toward a higher incidence of venous thromboembolism was also observed with this drug in a dose-dependent manner, and it has been reported that the incidence of death tended to be higher in the group that received 10 mg of this drug twice daily.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Cardiovascular events Cardiovascular events such as myocardial infarction may occur. Malignancy
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Uses**	<Rheumatoid arthritis> (deleted) <Ulcerative colitis> (deleted)
17. CLINICAL STUDIES (newly added)	17.3 Others Overseas post-market clinical study (A3921133 Study) An open-label, randomized, parallel-group, controlled study was conducted in 4 362 foreign patients with rheumatoid arthritis who were 50 years old or older and had at least 1 risk factor of cardiovascular events (such as smoking, hypertension, diabetes mellitus, and a history of coronary artery disease) to investigate the safety following administration of this drug (5 mg or 10 mg twice daily Note 1) or TNF inhibitors. The non-inferiority of the groups that received this drug to the TNF inhibitor group was not confirmed for either the incidence rate of major adverse cardiovascular events note 2) (MACE) or the incidence rate of malignancy (excluding non-melanoma skin cancer) as the co-primary endpoints.

Table Incidence rate of Major Adverse Cardiovascular Events (MACE)

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Incidence rate per 100 patient-years (95% CI)	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
Hazard ratio (95% CI)	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)[a]	

a: The upper limit of CI 95% for the hazard ratio of the groups of this drug combined to the TNF inhibitors group exceeded the preset non-inferiority margin of 1.8.

Table Incidence rate of Malignancy (excluding non-melanoma skin cancer)

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Incidence rate per 100 patient-years (95% CI)	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
Hazard ratio (95% CI)	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)[b]	

b: The upper limit of CI 95% for the hazard ratio of the groups that received this drug combined to the TNF inhibitors group exceeded the preset non-inferiority margin of 1.8.

The incidence rate of pulmonary embolism, deep vein thrombosis, and total death was as in the table below.

Table Incidence rate of Pulmonary Embolism and Deep Vein Thrombosis

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Pulmonary embolism	0.17 (0.08, 0.33)	0.50 (0.32, 0.74)	0.33 (0.23, 0.46)	0.06 (0.01, 0.17)
Deep vein thrombosis	0.21 (0.11, 0.38)	0.31 (0.17, 0.51)	0.26 (0.17, 0.38)	0.14 (0.06, 0.29)

Incidence rate per 100 patient-years (95% CI)

	5 mg BID N=1 455	10 mg BID N=1 456	This drug combined N=2 911	TNF inhibitors N=1 451
Total death	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)

Table Incidence rate of Total Death

Incidence rate per 100 patient-years (95% CI)

Note1) The approved dosage and administration of this drug for the

	indication of rheumatoid arthritis are oral administration of tofacitinib 5 mg twice daily. Note2) MACE was defined in the study as follows: · Cardiovascular death: Death due to acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular haemorrhage, death due to other cardiovascular causes: Peripheral artery disease. · Non-fatal myocardial infarction · Non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischaemia or haemorrhage.

5 Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria

Cefoperazone sodium/sulbactam sodium

Branded name	[1] Sulperazon for Intravenous Use 0.5 g, [2] Sulperazon for Intravenous Use 1 g, [3] Sulperazon Kit for Intravenous Use 1 g (Pfizer Japan Inc.), and the others
[Under Old instructions]	
Important Precautions	Since no methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction associated with this drug with reasonable certainty, the following measures should be taken.
Adverse Reactions **Clinically Significant adverse Reactions**	Shock, anaphylaxis (dyspnoea, etc.), acute coronary syndrome accompanying allergic reaction: Shock, anaphylaxis (dyspnoea, etc.), or acute coronary syndrome accompanying allergic reaction may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under New instructions]	
8.IMPORTANT PRECAUTIONS	Since no methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction associated with this drug with reasonable certainty, the following measures should be taken.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Shock, anaphylaxis (dyspnoea, etc.), acute coronary syndrome accompanying allergic reaction

6 Anthelmintics

Ivermectin

Branded name	Stromectol Tablets 3 mg (MSD K.K.)
[Under Old instructions]	
Important Precautions (newly added)	Disturbed consciousness may occur. Patients should be adequately informed of the caution required when engaging in hazardous machine operation such as driving a car.
Adverse Reactions Clinically Significant adverse Reactions (newly added)	Disturbed consciousness: If disturbed consciousness such as coma, depressed level of consciousness, or altered state of consciousness are observed, appropriate measures should be taken such as discontinuing 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 30 September 2021)
◎: Products for which EPPV was initiated after September 1, 2021

	Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
◎	Sotrovimab (genetical recombination) Xevudy for Intravenous Injection 500 mg	GlaxoSmithKline K.K.	September 29, 2021
◎	L-Lysine hydrochloride, L-arginine hydrochloride Lysakare Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
◎	Lutetium (^{177}Lu) oxodotreotide Lutathera Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
◎	Midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	September 27, 2021
◎	Rituximab (genetical recombination) *1 Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	September 27, 2021
◎	Sacubitril valsartan sodium hydrate*2 Entresto Tablets 100 mg, 200 mg	Novartis Pharma K.K.	September 27, 2021
◎	Sirolimus*3 Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	September 27, 2021
◎	Ibrutinib*4 Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	September 27, 2021
◎	Secukinumab (genetical recombination) [1] Cosentyx for s.c. injection 150 mg syringe [2] Cosentyx for s.c. injection 150 mg pen [3] Cosentyx for s.c. injection 75 mg syringe	Novartis Pharma K.K.	September 27, 2021
◎	Dinutuximab (genetical recombination) Unituxin I.V. injection 17.5 mg/5 mL	Ohara Pharmaceutical Co., Ltd.	September 22, 2021
◎	Imeglimin hydrochloride Twymeeg Tablets 500 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 16 2021
◎	Vericiguat Verquvo tablets 2.5 mg, 5 mg, 10 mg	Bayer Yakuhin Ltd.	September 15, 2021
	Fremanezumab (genetical recombination)	Otsuka Pharmaceutical	August 30,

	Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
	Ajovy Syringes for S.C. Injection 225 mg	Co., Ltd.	2021
	Givosiran sodium Givlaari Subcutaneous Injection 189 mg	Alnylam Japan K.K.	August 30, 2021
	Upadacitinib hydrate[*5] Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	August 25, 2021
	Dapagliflozin propylene glycolate hydrate[*6] Forxiga 5 mg, 10 mg tablets	AstraZeneca K.K.	August 25, 2021
	Selexipag[*7] Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	August 25, 2021
	Fentanyl citrate[*8] Fentos Tapes 0.5 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	August 25, 2021
	Upacicalcet sodium hydrate Upasita IV Injection Syringe for Dialysis 25 μg, 50 μg, 100 μg, 150 μg, 200 μg, 250 μg, 300 μg	Sanwa Kagaku Kenkyusho Co., Ltd.	August 20, 2021
	Teduglutide (genetical recombination) Revestive 3.8 mg for S.C. Injection	Takeda Pharmaceutical Company Limited.	August 18, 2021
	COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector) Vaxzevria Intramuscular Injection	AstraZeneca K.K.	August 16, 2021
	Erenumab (genetical recombination) Aimovig Subcutaneous injection Pens 70 mg	Amgen K.K.	August 12, 2021
	Risdiplam Evrysdi Dry Syrup 60 mg	Chugai Pharmaceutical Co., Ltd.	August 12, 2021
	Tazemetostat hydrobromide Tazverik tablets 200 mg	Eisai Co., Ltd.	August 16, 2021
	Larotrectinib sulfate Vitrakvi oral solution 20 mg/mL	Bayer Yakuhin Ltd.	August 6, 2021
	Simoctocog alfa (genetical recombination) Nuwiq For I.V. Injection 250, 500, 1000, 2000, 2500, 3000, 4000	Fujimoto Pharmaceutical Corporation	August 2, 2021
	Lyophilized human alpha1-proteinase inhibitor concentrate Lynspad for Intravenous Infusion 1000 mg	Grifols Therapeutics LLC.	July 27, 2021
	Casirivimab (genetical recombination), Imdevimab（genetical recombination） Ronapreve for Intravenous Infusion Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	July 22, 2021
	Rivaroxaban[*9] Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg	Bayer Yakuhin Ltd.	July 12. 2021
	Amikacin sulfate Arikayce (amikacin liposome inhalation suspension) 590 mg/8.4 mL	Insmed Incorporated.	July 7, 2021
	Larotrectinib sulfate	Bayer Yakuhin Ltd.	July 7,

Nonproprietary name / Branded name	Name of the MAH	Date of EPPV initiate
Vitrakvi capsules 25 mg, 100 mg		2021
Osilodrostat phosphate / Isturisa tablets 1 mg, 5 mg	Recordati Rare Diseases Japan KK	June 30, 2021
Incobotulinumtoxin A[*10] / Xeomin 50 units/100 units/200 units for Intramuscular injection	Teijin Pharma Limited.	June 23, 2021
Pemigatinib / Pemazyre Tablets 4.5 mg	Incyte Biosciences Japan G.K.	June 1, 2021
Inebilizumab (genetical recombination) / Uplizna for Intravenous Infusion 100 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2021
Upadacitinib hydrate[*11] / Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	May 27, 2021
Palonosetron hydrochloride / Aloxi I.V. injection 0.75 mg, Aloxi I.V. infusion bag 0.75 mg	Taiho Phamaceutical Co., Ltd.	May 27, 2021
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) / COVID-19 Vaccine Moderna Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 24, 2021
Ofatumumab (genetical recombination) [*12] / Kesimpta for s.c. injection 20 mg pen	Novartis Pharma K.K.	May 24, 2021
Polatuzumab vedotin (genetical recombination) / Polivy for Intravenous Infusion 140 mg, 30 mg	Chugai Pharmaceutical Co., Ltd.	May 19, 2021
Pabinafusp alfa (genetical recombination) / Izcargo for I.V. infusion 10 mg	JCR Pharmaceuticals Co., Ltd.	May 19, 2021
Denileukin diftitox (genetical recombination) / Remitoro for Intravenous Drip Infusion 300 μg	Eisai Co., Ltd.	May 19, 2021
Diclofenac etalhyaluronate sodium / Joyclu 30 mg intra-articular injection	Seikagaku Corporation	May 19, 2021
Anhydrous sodium sulfate/potassium sulfate/magnesium sulfate hydrate / Sulprep Combination Solution	Nihon Pharmaceutical Co., Ltd.	May 19, 2021
Galcanezumab (genetical recombination) / Emgality Subcutaneous Injection 120 mg Autoinjectors, Emgality Subcutaneous Injection 120 mg Syringe	Eli Lilly Japan K.K.	April 26, 2021
Idursulfase beta (genetical recombination) / Hunterase ICV Injection 15 mg	Clinigen K.K.	April 26, 2021
Baricitinib[*13] / Olumiant tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	April 23, 2021
Brigatinib / Alunbrig Tablets 30 mg, 90 mg	Takeda Pharmaceutical Company Limited.	April 23, 2021
Berotralstat hydrochloride	OrphanPacific, Inc.	April 23,

	Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
	Orladeyo Capsules 150 mg		2021
	Molidustat sodium Musredo tablets 5 mg, 12.5 mg, 25 mg, 75 mg	Bayer Yakuhin Ltd.	April 22, 2021
	Dimethyl sulfoxide Zymso Intravesical Solution 50%	Kyorin Pharmaceutical Co., Ltd.	April 21, 2021
	Anamorelin hydrochloride Adlumiz Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	April 21, 2021
	Acalabrutinib Calquence capsules 100 mg	AstraZeneca K.K.	April 21, 2021

*1 Systemic scleroderma

*2 Hypertension

*3 Refractory lymphatic diseases (lymphangioma (lymphatic malformation), lymphangiomatosis, Gorham's disease, lymphangiectasia)

*4 Chronic graft versus host disease after haematopoietic stem cell transplantation (when steroids are not sufficiently effective)

*5 Atopic dermatitis that has not responded adequately to conventional treatments

*6 Chronic kidney disease

*7 Chronic thromboembolic pulmonary hypertension inoperable or persistent/recurrent after interventional treatment

*8 Pain relief in cancers accompanied by moderate to severe pain difficult to treat with non-opioid analgesics (limited to use as a switch from other opioid analgesics)

*9 Treatment and reduction in the risk of recurrence of venous thromboembolism

*10 Leg spasm

*11 Psoriatic arthritis in patients who have responded inadequately to conventional therapy

*12 Prevention of relapse and delaying the accumulation of physical disability in patients with relapsing-remitting multiple sclerosis and patients with active secondary progressive multiple sclerosis

*13 SARS-CoV2 pneumonia (limited to patients requiring supplemental oxygen)