Pharmaceuticals and Medical Devices Safety Information

No. 377 November 2020

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 (https://www.mhlw.go.jp, only in Japanese).

Available information is listed here

Your cooperation with the survey on the PMDA Medi-navi utilization and others is encouraged.

From November 26 to December 13, 2020, utilization of the PMDA Medi-navi will be surveyed in the medical professionals who use the service.

The survey can be answered in the page accessed from the URL in the delivered Medi-navi mails or the QR code below.

Register and answer the survey here.

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Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

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No. 377 November 2020

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of providers of medical care and pharmaceutical products.

If providers of medical care and pharmaceutical products 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 providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
AST	Aspartate aminotransferase
CRP	C-reactive protein
DLST	Drug-induced lymphocyte stimulation test
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HPV	Human papilloma virus
LD	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SJS	Stevens-Johnson syndrome
SpO_2	Percutaneous oxygen saturation
WBC	White blood cell

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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 System since 2014.

In this Relief System, a total of 24 565 cases have been granted relief benefits since the establishment of the Relief System in 1980 until the end of fiscal year (FY) 2019.

2. Awareness of the Relief System for Adverse Drug Reactions

Awareness of the Relief System among the general public in FY 2019 was 30.2% in total according to the FY 2019 survey: 9.4% answered that they "were aware" of the Relief System and 20.8% 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 83.5% in total: 59.0% answered that they "were aware" of the Relief System and 24.5% answered that they "have heard about" the Relief System. By occupational category, awareness was 91.9% among physicians, 96.6% among pharmacists, 63.0% among nurses, and 81.5% 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 11.4% overall: 13.8% among physicians, 13.3% among pharmacists, 7.8% among nurses, and 6.9% 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 included in April 2016 to grasp the sources of information related to the Relief System. The FY 2019 results showed "Physician" in 502 answers (30.4%), "Others" (the Internet) in 277 answers (16.8%), "Newspaper/TV, etc." in 173 answers (10.5%) and "Pharmacist" in 166 answers (10.0%) in descending order (multiple answers acceptable) [Note 2)].

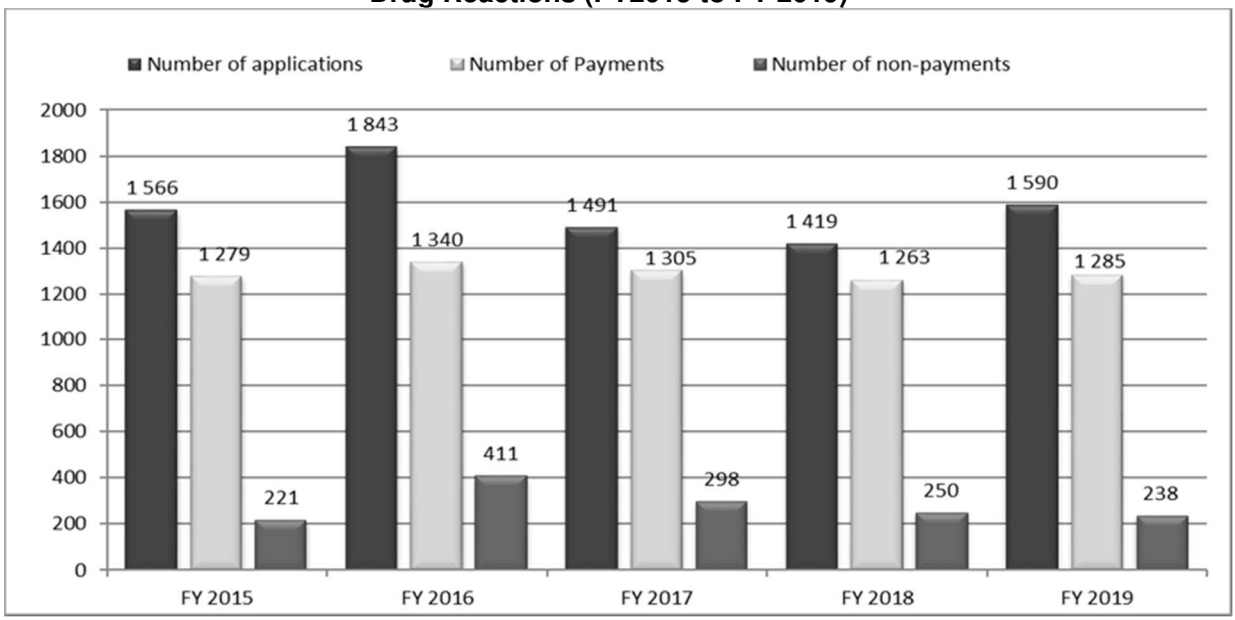
In June 2014, a field for information on the Relief System was newly added to the form of the Pharmaceuticals and Medical Devices Safety Information Report, the form for healthcare professionals to report adverse drug reactions. The field lists options such as "the patient intends to claim" and "the 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. 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 2015 and FY 2019 are shown in Figure 1. In FY2019, the number of applications was 1 590, the number of payments was 1 285, and the number of non-payments was 238. The ratios between payment and non-payment and details of reasons for non-payments from FY 2015 to FY 2019 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 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 2019 was 72.3%.

Figure 1. Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2015 to FY 2019)

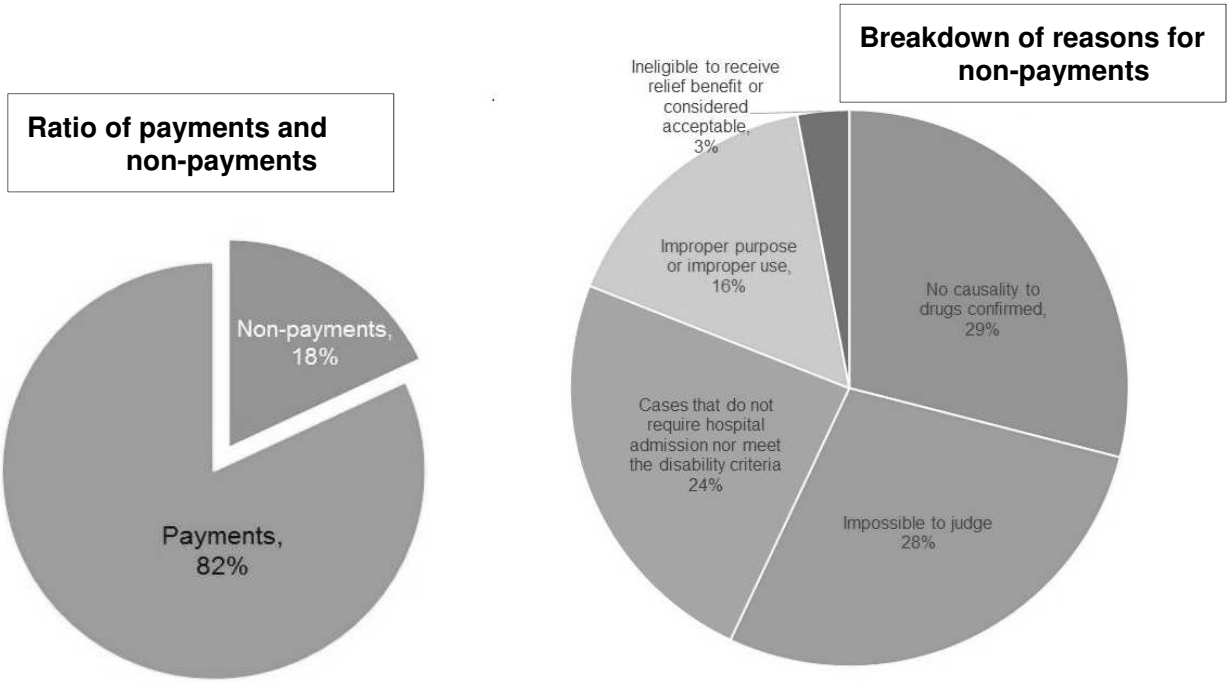


(Graph description)

*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 2015 and FY 2019



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 this 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/relief-services/outline/0001.html) (only in Japanese).

[Types and amounts of relief benefits (as of April 1, 2020)]
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, etc.
  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, etc.

Lump-Sum Benefits for Bereaved Family (7 372 800 yen)
• Benefits are provided to bereaved families for condolence and sympathy following death due to ADRs, etc. of a family member who is not the main provider.

Funeral Expenses (209 000 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 drug-induced liver disorder due to a kampo medicine, for which medical expenses and medical allowance benefits were provided

A woman in her 40s developed liver disorder following administration of Tsumura Daisaikoto Extract Granules (prescription) and received inpatient treatment. Medical expenses and medical allowance benefits were provided.

<Case 2> A case of thrombotic thrombocytopenic purpura due to clopidogrel tablets, for which medical expenses, medical allowance, bereaved family benefits, and funeral expenses benefits were provided

A man in his 70s developed thrombotic thrombocytopenic purpura after using Pravix Tablets (clopidogrel) and received inpatient treatment. He died from myocardial infarction secondary to thrombotic thrombocytopenic purpura. Medical allowance, bereaved family pension, and funeral expenses benefits were provided.

<Case 3> A case of toxic optic neuropathy due to ethambutol, which led to a disability status, and disability pension benefits were provided

A man in his 70s developed toxic optic neuropathy following use of Ebutol Tablets (ethambutol) and became visually impaired. Disability pension benefits were provided.

<Case 4> A case of oculomucocutaneous syndrome (Stevens-Johnson syndrome/SJS) due to an OTC drug. Medical expenses and medical allowance benefits were provided.

A woman in her 40s experienced oculomucocutaneous syndrome (SJS) following use of Pabron Gold 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 1 418[Note 4)] non-payment cases from FY 2015 to FY 2019, the reason for nonpayment in approximately 16% of them was that the proper purpose or method of use of the drug could not be confirmed (Figure 2). The cases for which the method of use was not considered proper in the past year are introduced in this section. Table 1 shows the most common drugs for which the method of use was not considered proper.

Table 1. Number of cases in which the method of use of the drug was not considered proper (FY 2015 to FY 2019)

Name of causative drug	FY 2015	FY 2016	FY 2017	FY 2018	FY 2019	Total (cases)
Lamotrigine	23	24	9	12	15	83
Thiamazole	5	3	1	3	2	14
Lithium carbonate	1	8	0	1	3	13
Methotrexate	2	0	1	1	4	8
Propofol	0	0	1	0	2	3
Other	23	19	16	27	20	105
Total (cases)	54	54	28	44	46	226

(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 package insert once again and pay attention to the dosage and administration when using drugs.

<Case> A case of erythema multiform type drug eruption due to lamotrigine

A woman in her 20s used Lamictal Tablets (lamotorigine) for bipolar II affective disorder without co-administration of sodium valproate, and with drugs other than those inducing glucuronidation. Lamotorigine was started from a daily dose of 25 mg, which was increased to 50 mg/day after 7 days. Therefore, this drug use was not considered proper.

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 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)] for 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. Please make sure to read the package insert carefully before use.

Figure 3 shows examples of dosage and administration when used for suppression of recur-rent/relapse mood episodes in bipolar disorder in adults. Please refer to the package insert of lamotrigine for other examples of closely regulated dosage and administration.

When used for suppression of recurrent/relapse mood episodes in bipolar disorder
Source: Package insert of Lamictal Tablets (revised in October 2018)

Figure 3 Examples of concomitant drugs with lamotrigine

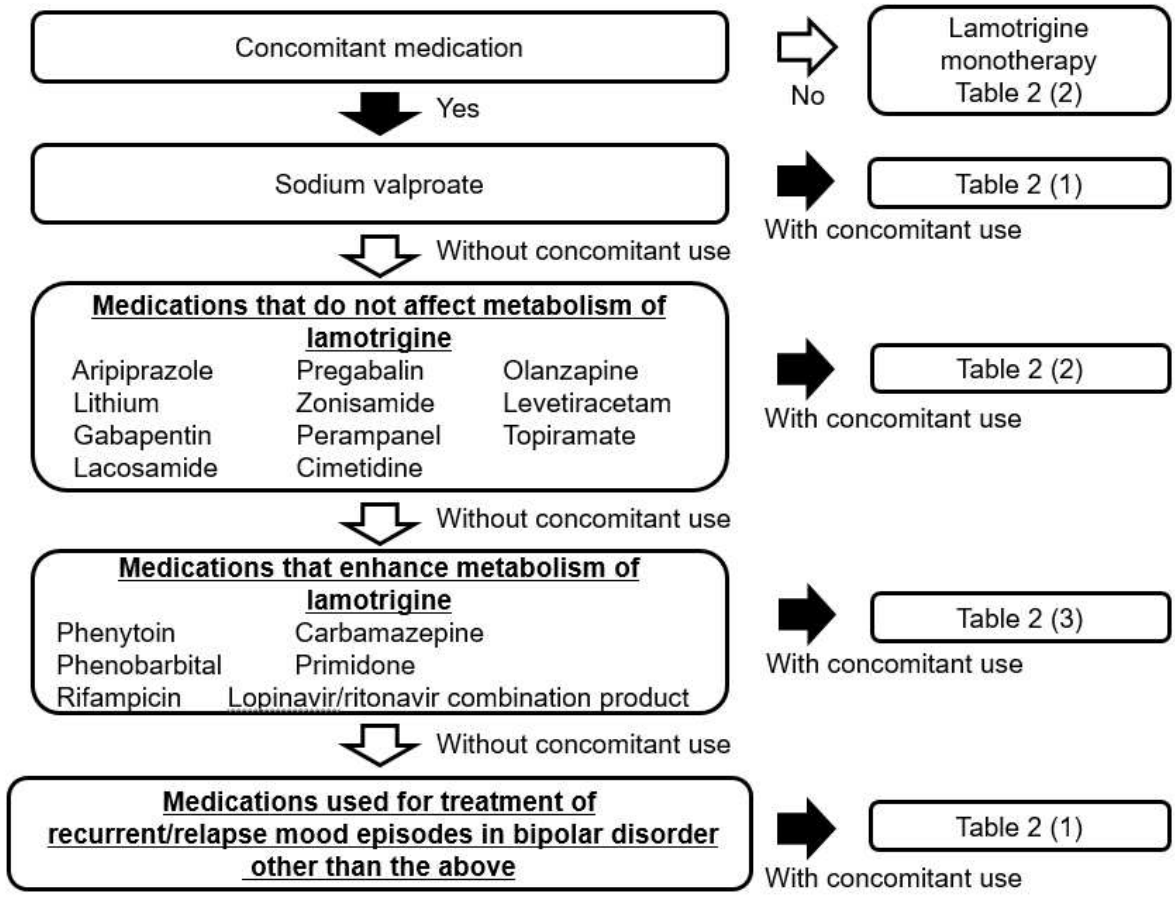


Table 2 Starting dose of lamotrigine

	Week 1/2	Week 3/4	Week 5	After Week 6
(1)	25 mg once every 2 days	25 mg/day	50 mg/day	100 mg/day (Maximum 200 mg/day) (Dose should be increased by up to 50 mg/day at a 1-week interval and longer)

	Week 1/2	Week 3/4	Week 5	After Week 6
(2)	25 mg/day	50 mg/day	100 mg/day	200 mg/day (Maximum 400 mg/day) (Dose should be increased by up to 100 mg/day at a 1-week interval and longer)

	Week 1/2	Week 3/4	Week 5	Week 6	After Week 7
(3)	50 mg/day	100 mg/day	200 mg/day	300 mg/day	300 mg/day to 400 mg/day (Maximum 400 mg/day) Dose should be increased by up to 100 mg/day at a 1-week interval and longer

(2) Cases where the required tests were not conducted

If the package inserts specify that certain tests must be conducted for use of drugs and these tests are not conducted, the use will 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 agranulocytosis due to thiamazole

A woman in her 50s. Since no blood tests including differential count of leukocytes had been conducted for 41 days until agranulocytosis was observed after the start of Mercazole Tablets (thiamazole) administration, the case was not approved as proper use.

Description in the package insert of Mercazole Tablets (partial excerpt)

Warnings

It has also been reported that there were cases where serious agranulocytosis mostly occurred within 2 months after the start of administration and resulted in death. In principle, a blood test including differential count of leukocytes should be conducted once every 2 weeks for at least 2 months after the start of administration and periodically thereafter. When any abnormalities such as decreasing tendency of granulocytes are observed, administration should be discontinued immediately and appropriate measures should be taken. Similar caution is required when administration of the drug is resumed if it has been discontinued once.

<Case 2> A case of disturbed consciousness resulting from hyperglycaemia due to olanzapine

A woman in her 30s. She had gained approximately 20 kg in the past 2 years and despite the high necessity for being alert to obesity and for blood sugar measurements indicated by such weight increase, no blood sugar measurements were performed during the 4 months of Zyprexa Tablets (olanzapine) administration. Thus, the case was not approved as proper use.

Description in the package insert of Zyprexa Tablets (partial excerpt)

Warnings

Clinically significant adverse reactions such as diabetic ketoacidosis or diabetic coma may occur and could result in death. Patients should be closely monitored during treatment with this drug through methods such as blood sugar measurements.

Important Precautions

Administration of this drug may result in a fatal clinical course beginning from marked elevation in blood sugar leading to diabetic ketoacidosis or diabetic coma. Patients should be closely monitored during administration through blood sugar measurements and for thirst, excessive drinking, polyuria, or pollakiuria. In patients with risk factors of diabetes mellitus such as hyperglycaemia and obesity particularly, blood sugar may become elevated and rapidly deteriorate the metabolic status.

(3) Cases of use in patients falling under Contraindications

There are also cases where the drug was used (continuously) in patients falling under 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 severely impaired renal function

A woman in her 70s. Rheumatrex Capsules (methotrexate) was continuously used while the patient's renal function was severely impaired. Platelet counts, RBC, and WBC gradually declined until marked pancytopenia occurred and administration of Rheumatrex Capsules was discontinued. The patient subsequently developed aplastic anaemia and sepsis in conjunction with pancytopenia and died. Because methotrexate is contraindicated in patient with renal disorder, the case was not approved as proper use.

Description in the package insert of methotrexate (partial excerpt)

Contraindications (this drug should not be administered to the following patients)

5) Patients with renal disorder (Adverse reactions may be more severe.)

(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 firm 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 drug-induced liver disorder due to loxoprofen and rebamipide

A woman in her 60s. Since the patient took the residual Loxonin Tablets (loxoprofen) and Mucosta Tablets (rebamipide) that were previously prescribed by her physician at her own discretion, this 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 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 this 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 Relief 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 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 applicable 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)
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 before using Drugs and to use them properly. Please note that cases in which Drugs are not used properly may not be applicable to receive relief benefits under the Relief System even if the adverse health effects are suspected to have been caused by ADRs related to the Drugs. On the other hand, off-label uses which are widely known in medical practice, such as those described in the guidelines, may be covered for relief benefits.

If ADRs, etc. occur 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 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.
http://www.pmda.go.jp/index.html (only in Japanese)

The following consultation service in regard to this 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 2019 Awareness Survey on the Relief System for Adverse Drug Reaction
http://www.pmda.go.jp/relief-services/adr-sufferers/0023.html (only in Japanese)

Note 2) From: FY 2019 Relief Service Committee (Pharmaceuticals and Medical Devices Agency)
https://www.pmda.go.jp/about-pmda/advisory-council-information/relief-services/0045.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 2020, there have been 315 of the total 512 patients who had been reviewed who were determined eligible for the Relief System for whom a causal relationship to HPV vaccines could not be ruled out.

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) 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 are possibly 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
Year	2016	2017	2018	2019	Total	
Number of claims	334 cases	141 cases	86 cases	58 cases	796 cases	
Number of Payments	314 cases	223 cases	111 cases	75 cases	749 cases	

(Source: PMDA Annual Report FY 2019
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 on January 14, 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 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 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

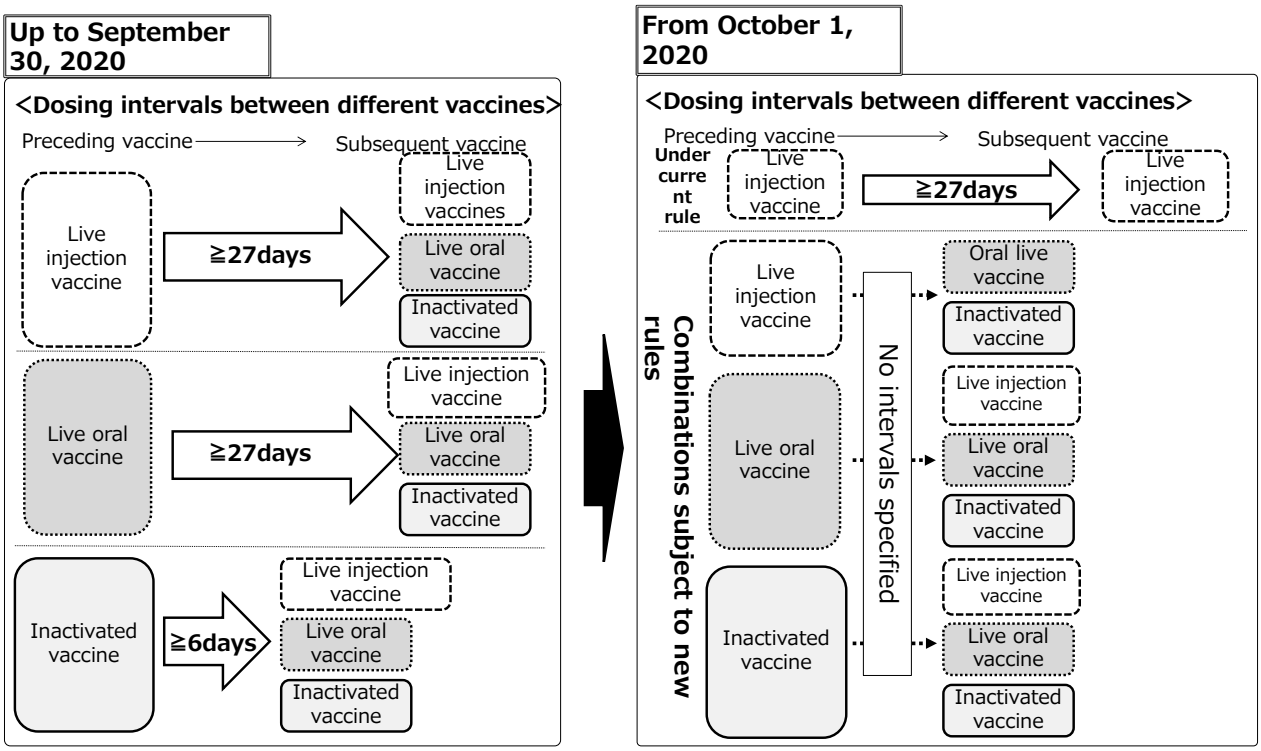
Revision of Dosing Intervals between Different Vaccines

1. Introduction

The package inserts of vaccines had specified dosing intervals between different vaccines as 27 days or longer after live vaccines and 6 days or longer after inactivated vaccines until September 30, 2020. Then, these restrictions were lifted by the revision of the package inserts on October 1, 2020, except for dosing between injectable live vaccines, for which the current restriction of 27 days or longer was to be maintained.

This section will outline the revision of the time intervals between administrations of different vaccines, for which the precautions of the package insert was revised on October 1, 2020, as well as the reporting form for suspected adverse drug reactions which was updated in line with the revision of the vaccine dosing intervals.

The revision of the time intervals between dosing of different vaccines was introduced in No. 375 (August 2020) of the Pharmaceuticals and Medical Devices Safety Information (PMDSI) prior to the implementation. Please refer to No. 375 using the link below for the background of the revision of precautions in the package insert.
https://www.pmda.go.jp/files/000236193.pdf



<Note>

- **For several days after vaccination, symptoms such as pyrexia or injection site swelling may appear. Absence of pyrexia, injection site swelling, or other symptoms indicative of compromised patients' conditions should be ensured before vaccination even within intervals permitted by the package insert.**
- **Simultaneous vaccination is acceptable when specifically permitted by the physician.**
- **For intervals for multiple dosing of the same vaccine, instructions in the package insert should be followed.**

2. Outline of Revision of Dosing Intervals between Different Vaccines

On October 1, 2020, package inserts for vaccines were revised to lift the restrictions on dosing intervals between different vaccines except for dosing between injectable live vaccines (Table 1). The revision should be noted among medical professionals who consider vaccination schedules.

For multiple dosing of the same type of vaccines, an interval of a certain period of time should be placed according to the dosage and administration or other related information in the package insert of the specific vaccine product.

Table 1. Revision of package insert (model example)

For live injectable vaccines — Revised language is underlined.

Current	Revision
Precautions of Dosage and Administration Dosing intervals with other vaccine preparations A person recently administered with another live vaccine usually should receive this vaccine at least 27 days apart. A person recently administered with an inactivated vaccine should usually receive this vaccine at least 6 days apart. Conditionally, this product may be vaccinated simultaneously when the physician considers it necessary.	Precautions of Dosage and Administration Dosing intervals with other live vaccines (injection) A person recently administered with another live vaccine (injection) usually should receive this vaccine at least 27 days apart. (deleted) Simultaneous vaccination This product may be vaccinated simultaneously with other vaccines when the physician considers it necessary.

For inactivated vaccines and live oral vaccines — Revised language is underlined.

Current	Revision
Precautions of Dosage and Administration Dosing intervals with other vaccine preparations A person recently administered with a live vaccine usually should receive this vaccine at least 27 days apart. A person recently administered with another inactivated vaccine should usually receive this vaccine at least 6 days apart. Conditionally, this product may be vaccinated simultaneously when the physician considers it necessary.	Precautions of Dosage and Administration (deleted) Simultaneous vaccination This product may be vaccinated simultaneously with other vaccines when the physician considers it necessary.

3. Updated reporting form for suspected adverse vaccine reactions

In line with the revised vaccine dosing intervals, the reporting form for suspected post-vaccination adverse reactions was updated (Table 2) by the Partial Amendment of Handling of Reports of Suspected Adverse Reactions by Routine Vaccination, etc., (dated September 24, 2020). The Points to be Considered in the reporting form for suspected post-vaccination adverse reactions had so far requested types of vaccine, etc., as the Vaccination Status within the Past 1 Month. The entry instructions were also revised on October 1, 2020 to request vaccination dates as well to grasp the time intervals between different types of vaccines.

In reporting suspected adverse reactions to vaccines, reporters are requested to add information on the vaccination dates in addition to the types of vaccines administered.

4. Closing Remark

On October 1, 2020, the Routine Immunization Guidelines were amended and the package inserts of vaccines were revised for revision of the dosing intervals between different vaccines. On the other hand, the previous interval of 27 days or longer between live injectable vaccines are retained.

The revision should be noted among medical professionals who consider vaccination schedules. For multiple dosing of the same type of vaccines, an interval of a certain period of time should be placed between individual doses according to the dosage and administration or other related information in the package insert of the specific vaccine product.

MHLW/PMDA will continue to gather safety information on vaccines including suspected adverse reaction reports and to adopt safety measures. Alerting the vaccine recipients and reporting suspected adverse reactions to the vaccines by healthcare professionals are encouraged and appreciated.

[Reference]

Partial Amendment of Handling of Reports of Suspected Adverse Reactions by Routine Vaccination, etc., (dated September 24, 2020)
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/kanrentuuti.html
(only in Japanese)

Report form
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r01youshiki_02.pdf
(only in Japanese)

Entry instructions
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r01youshiki_03.pdf
(only in Japanese)

Report entry application (National Institute of Infectious Diseases)
http://www.nih.go.jp/niid/ja/vaccine-j/6366-vaers-app.html (only in Japanese)

Table 2 Reporting form for suspected post-vaccination adverse reactions (only in Japanese)

予防接種後副反応疑い報告書

予防接種法上の定期接種・任意接種の別		□ 定期接種		□ 任意接種		
患者（被接種者）	氏名又はイニシャル（姓・名）	フリガナ （定期の場合は氏名、任意の場合はイニシャルを記載）	性別	1 男 2 女	接種時年齢	歳 月
	住所	都道府県 区市町村	生年月日	T H S R 年 月 日生		
報告者	氏名	1 接種者（医師） 2 接種者（医師以外） 3 主治医 4 その他（ ）				
	医療機関名		電話番号			
	住所					
接種場所	医療機関名					
	住所					

ワクチン	ワクチンの種類（②～④は、同時接種したものを記載）	ロット番号	製造販売業者名	接種回数
	①			① 第 期（ 回目）
	②			② 第 期（ 回目）
	③			③ 第 期（ 回目）
	④			④ 第 期（ 回目）

接種の状況				
	接種日	平成・令和 年 月 日 午前・午後 時 分	出生体重	グラム（患者が乳幼児の場合に記載）
	接種前の体温	度 分	家族歴	
	予診票での留意点（基礎疾患、アレルギー、最近1か月以内のワクチン接種や病気、服薬中の薬、過去の副作用歴、発育状況等） 1 有 → 2 無			

症状の概要				
	症状	定期接種の場合で次頁の報告基準に該当する場合は、ワクチンごとに該当する症状に○をしてください。 急性散在性脳脊髄炎又はギラン・バレ症候群に該当する場合は、各調査票を記入のうえ、提出してください。 報告基準にない症状の場合又は任意接種の場合（症状名： ）		
	発生日時	平成・令和 年 月 日 午前・午後 時 分		
	本剤との因果関係	1 関連あり 2 関連なし 3 評価不能	他要因（他の疾患等）の可能性の有無	1 有 → 2 無
	概要（症状・徴候・臨床経過・診断・検査等）			
	○製造販売業者への情報提供 ： 1 有 2 無			

症状の程度		
	1 重い →	1 死亡 2 障害 3 死亡につながるおそれ 4 障害につながるおそれ 5 入院（病院名： 医師名： 平成・令和 年 月 日 入院 ／ 平成・令和 年 月 日 退院） 6 上記1～5に準じて重い 7 後世代における先天性の疾病又は異常
	2 重くない	

症状の転帰		
	転帰日	平成・令和 年 月 日
	1 回復 2 軽快 3 未回復 4 後遺症（症状： ） 5 死亡 6 不明	

報告者意見	
報告回数	1 第1報 2 第2報 3 第3報以後

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated October 6, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Vonoprazan fumarate

Branded name (name of company)	Takecab Tablets 10 mg, 20 mg (Takeda Pharmaceutical Company Limited.)
Therapeutic category	Agents for peptic ulcer
Indications	Treatment of gastric ulcer, duodenal ulcer, reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration; and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration Adjunct therapy to *Helicobacter pylori* eradication in the following: Gastric or duodenal ulcer, gastric mucosa associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage gastric cancer, or *Helicobacter pylori* gastritis

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **<Common to all indications>** **(newly added)**	<u>Shock, anaphylaxis</u> <u>Hepatic impairment</u>
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 2017 to March 2020) Cases involving shock or anaphylaxis: 1 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 14 000 000 Japanese market launch: February 2015

Case

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		No.
1	Female 30s	Reflux oesophagitis (none)	20 mg 1 day ↓ Discontinuation	**Anaphylaxis** Medical history, predisposition, etc.: None Day 1 of administration (day of discontinuation): The patient had heartburn for a few weeks and received gastroscope at another hospital. Reflux oesophagitis was diagnosed and vonoprazan fumarate was prescribed to be taken before bed. The patient took the prescribed drug the same day. 1 day after dis-continuation: The patient experienced symptoms of pruritus and nausea 3 hours after taking vonoprazan fumarate the previous day and visited the emergency department. With generalised flushing, decreased blood pressure (87/57), and percutaneous oxygen saturation (SPO_2) 98%, anaphylactic shock was assumed and 0.3 mg of adrenaline was administered intramuscularly. The patient was admitted to the hospital. Vonoprazan fumarate was discontinued with the dosing on the previous day. The patient was treated with a drip infusion of methylprednisolone 125 mg/day (2 days). Date unknown: Generalised itching persisted. Erythema on the thighs was noted. 3 days after dis-continuation: Symptoms were resolving. The patient was discharged from the hospital. Date unknown: DLST was performed after hospital discharge: Vonoprazan fumarate 272 cpm (+), control 114 cpm The patient has not visited the hospital since discharge.

Laboratory test values:

	Day 1 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	10 days after Discontinuation	Date unknown
WBC (μL)	16 100	–	8 400	6 249	–
Lymphocyte	3 139	–	1 537	1 277	–
LD (u/L)	300	–	203	182	–
AST (IU/L)	36	–	15	13	–
CRP (mg/dL)	0.06	–	0.75	0.2	–
Blood pressure	–	87/57	–	–	–
SPO_2 (%)	–	98	–	–	–
DLST (cpm): Vonoprazan fumarate	–	–	–	–	272 (+)
DLST (cpm): Control	–	–	–	–	114

Suspect concomitant drugs: None
Concomitant drugs: None

4
Revision of Precautions (No.317)

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 October 6, 2020.

1 Agents for peptic ulcer
Vonoprazan fumarate

Branded name	Takecab Tablets 10 mg, 20 mg (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions	Shock, anaphylaxis Hepatic impairment
<Common to all indications>	
(newly added)	

2 Antimetabolic agents
Cytarabine (excluding 400 mg and 1 g preparations)

Branded name	Cylocide Injection 20 mg, 40 mg, 60 mg, 100 mg, 200 mg (Nippon Shinyaku Co., Ltd.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Eye symptom and cutaneous symptom are known characteristic adverse reactions to this drug. Eye symptom includes conjunctivitis, eye pain, photophobia, eye discharge, conjunctival hyperaemia, and corneal ulcer. These symptoms may be prevented or reduced with corticosteroid ophthalmic solution. Cutaneous symptom includes rash, redness, and erythema (frequently accompanied by intense pain) in the distal portion of the extremities. These symptoms may be reduced with corticosteroid.
(newly added)	
11. ADVERSE REACTIONS	**Cytarabine syndrome**: Cytarabine syndrome may occur as pyrexia, muscle pain, bone pain and occasionally as rash maculo-papular, chest pain, conjunctivitis, and malaise. Patients should be carefully monitored. The syndrome usually occurs 6 to 12 hours following administration of this drug. If any of these symptoms occur, appropriate measures should be taken such as administration of corticosteroid.
11.1 Clinically Significant Adverse Reactions	
(newly added)	
13. OVERDOSAGE	(deleted)
13.1 Symptoms	

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

Tazobactam/piperacillin hydrate

Branded name	Zosyn Intravenous Injections 2.25, 4.5, Zosyn Intravenous Infusions Bag 4.5 (TAIHO Phamaceutical Co., Ltd.), and the others
[Under Old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	**Hypokalaemia**: Hypokalaemia accompanied by malaise, feelings of weakness, arrhythmia, or convulsion may occur. Patients should be carefully monitored through methods such as periodic examinations. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4 Other antibiotic preparations

[1] Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
[2] Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Branded name	[1] Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited.) [2] Vonopion Pack (Takeda Pharmaceutical Company Limited.)
[Under Old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	(Vonoprazan fumarate) Shock or anaphylaxis 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. Hepatic impairment 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.

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 2020)

◎: Products for which EPPV was initiated after September 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Trastuzumab deruxtecan (genetical recombination) *1 Enhertu For Intravenous Drip Infusion 100 mg	Daiichi Sankyo Co., Ltd.	September 25, 2020
◎	Ravulizumab (genetical recombination) *2 Ultomiris for Intravenous Infusion 300mg	Alexion Pharmaceuticals, Inc.	September 25, 2020
◎	Tildrakizumab (genetical recombination) Ilumya Subcutaneous Injection 100 mg Syringe	Sun Pharma Japan Limited	September 23, 2020
◎	Siponimod fumaric acid Mayzent tablets 0.25 mg, 2 mg	Novartis Pharma K.K.	September 14, 2020
◎	Ferric carboxymaltose Ferinject solution for injection/infusion 500 mg	Zeria Pharmaceutical Co., Ltd.	September 1, 2020
	Isatuximab (genetical recombination) Sarclisa 100 mg I.V. Infusion, Sarclisa 500 mg I.V. Infusion	Sanofi K.K.	August 31, 2020
	Indacaterol acetate/glycopyrronium bromide/ mometasone furoate Enerzair medium dose inhalation powder with hard capsules, Enerzair high dose inhalation powder with hard capsules	Novartis Pharma K.K.	August 26, 2020
	Indacaterol acetate/mometasone furoate Atectura low dose inhalation powder with hard capsules, Atectura medium dose inhalation powder with hard capsules, Atectura high dose inhalation powder with hard capsules	Novartis Pharma K.K.	August 26, 2020
	Sacubitril valsartan sodium hydrate Entresto Tablets 50 mg, 100 mg, 200 mg	Novartis Pharma K.K.	August 26, 2020
	Capmatinib hydrochloride hydrate Tabrecta tablets 150 mg, 200 mg	Novartis Pharma K.K.	August 26, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Satralizumab (genetical recombination) Enspryng Syringes for Subcutaneous Injection 120 mg	Chugai Pharmaceutical Co., Ltd.	August 26, 2020
Daprodustat Duvroq Tablets 1 mg, 2 mg, 4 mg, 6 mg	GlaxoSmithKline K.K.	August 26, 2020
Vadadustat Vafseo Tablets 150 mg, 300 mg	Mitsubishi Tanabe Pharma Corporation	August 26, 2020
Opicapone Ongentys Tablets 25 mg	Ono Pharmaceutical Co., Ltd.	August 26, 2020
Tirabrutinib hydrochloride*3 Velexbru Tablets 80 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2020
Vonicog alfa (genetical recombination) Vonvendi Intravenous 1300	Shire Japan KK	August 17, 2020
Remimazolam besilate Anerem 50 mg for I.V. Injection	Mundipharma K.K.	August 7, 2020
Posaconazole Noxafil for Intravenous Infusion 300 mg	MSD K.K.	July 21, 2020
Lemborexant Dayvigo Tablets 2.5 mg, 5mg, 10 mg	Eisai Co., Ltd.	July 6, 2020
Fluticasone propionate/formoterol fumarate hydrate Flutiform 50 Aerosol 56 puffs, 120 puffs	Kyorin Pharmaceutical Co.,Ltd.	June 29, 2020
Semaglutide (genetical recombination) Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD	Novo Nordisk Pharma Ltd.	June 29, 2020
Tolvaptan*4 Samsca tablets 7.5 mg, 15 mg, 30 mg, Samsca OD tablets 7.5 mg, 15 mg, 30 mg, Samsca granules 1%	Otsuka Pharmaceutical Co., Ltd.	June 29, 2020
Landiolol hydrochloride*5 Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	June 29, 2020
Levothyroxine sodium hydrate Thyradin-S I.V. Injection 200 μg	Aska Pharmaceutical. Co., Ltd.	June 29, 2020
Delgocitinib Corectim Ointment 0.5%	Japan Tabacco Inc.	June 24, 2020
Melatonin Melatobel granules 0.2% for pediatric	Nobelpharma Co., Ltd.	June 23, 2020
Insulin lispro (genetical recombination) Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD Lyumjev Injection 100 U/mL	Eli Lilly Japan K.K.	June 17, 2020
Insulin glargine (genetical recombination)/lixisenatide Soliqua Injection SoloStar	Sanofi K.K.	June 8, 2020
Tepotinib hydrochloride hydrate Tepmetko Tablets 250 mg	Merck Biopharma Co., Ltd	June 1, 2020
Nintedanib ethanesulfonate*6	Boehringer Ingelheim	May 29,

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Ofev capsules 100 mg, 150 mg	Japan, Inc.	2020
Darolutamide Nubeqa tablets 300 mg	Bayer Yakuhin Ltd	May 26, 2020
Trastuzumab deruxtecan (genetical recombination) Enhertu for intravenous drip infusion 100 mg	Daiichi Sankyo Co., Ltd.	May 25, 2020
Brolucizumab (genetical recombination) Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	May 25, 2020
Dotinurad Urece Tablets 0.5 mg, 1 mg, 2 mg	FUJIYAKUHIN Co., Ltd.	May 25, 2020
Cabozantinib malate Cabometyx tablets 20 mg, 60 mg	Takeda Pharmaceutical Company Limited.	May 22, 2020
Borofalan (^{10}B) Steboronine 9000 mg/300 mL for infusion	STELLA PHARMA CORPORATION	May 20, 2020
Tirabrutinib hydrochloride Velexbru Tablets 80 mg	Ono Pharmaceutical Co., Ltd.	May 20, 2020
Viltolarsen Viltepso Injection 250 mg	Nippon Shinyaku Co., Ltd.	May 20, 2020
Sodium zirconium cyclosilicate hydrate Lokelma 5 g/10 g powder for suspension (single-dose package)	AstraZeneca K.K.	May 20, 2020
Remdesivir Veklury for Intravenous Injection 100 mg	Gilead Sciences Inc.	May 11, 2020
Upadacitinib hydrate Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	April 24, 2020
Posaconazole Noxafil Tablets 100 mg	MSD K.K.	April 24, 2020
Lurasidone hydrochloride Latuda tablets 20 mg, 40 mg, 60 mg, 80 mg	Sumitomo Dainippon Pharma Co., Ltd.	April 22, 2020
Dinoprostone Propess vaginal inserts 10 mg	Ferring Pharmaceuticals Co., Ltd.	April 2, 2020

*1 HER2 positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy

*2 Atypical hemolytic uremic syndrome

*3 Primary macroglobulinaemia and lymphoplasmacytic type lymphoma

*4 Improvement of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

*5 Tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) associated with sepsis

*6 Progressive fibrosing interstitial lung disease