

# Pharmaceuticals and Medical Devices Safety Information

No. 367 October 2019

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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 in Japanese).

Available information is listed here 

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

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



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

# Pharmaceuticals and Medical Devices Safety Information

No. 367 October 2019

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

## [ Outline of Information ]

No.	Subject	Measures	Outline of Information	Page
1	<b>Publication of Risk Management Plan (RMP) Materials on the PMDA website</b>		Materials prepared/provided as part of additional risk minimization activities of RMP (RMP materials) have been published on the PMDA website since April of this year. This section will introduce the activities performed by MHLW/PMDA to facilitate the use of RMP and RMP materials.	4
2	<b>Summary of the Relief System for Adverse Drug Reactions and Request for Co-operation with the System</b>		This is to introduce the summary of the Relief System for Adverse Drug Reactions to share the common knowledge of this system since its recognition rate was low among the general public in FY2018.	9
3	<b>Important Safety Information</b>	P C	Baricitinib and Osimertinib mesilate. Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated September 24, 2019, the contents of important revisions and case summaries that served as the basis for these revisions will be presented in this section.	22
4	<b>Revision of Precautions (No. 307)</b>	P	Baricitinib (and 14 others)	31
5	<b>List of Products Subject to Early Post-marketing Phase Vigilance</b>		List of products subject to Early Post-marketing Phase Vigilance as of August 31, 2019.	36

*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

ADRs	Adverse drug reactions
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BUN	Blood urea nitrogen
Cl	Chlorine
CRP	C-reactive protein
CT	Computed tomography
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
Hb	Hemoglobin
HPV	Human papilloma virus
IVIg	Intravenous immunoglobulin
K	Potassium
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Na	Sodium
PD	Pupillary distance
PFSB/ELD	Evaluation and Licensing Division, Pharmaceuticals and Food Safety Bureau
PFSB/SD	Safety Division, Pharmaceuticals and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB/ELD	Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
RMP	Risk Management Plan
SI	Stimulation index
SJS	Stevens-Johnson syndrome
SpO2	Oxygen saturation
TEN	Toxic epidermal necrolysis
γ-GTP	Gamma-glutamyl transpeptidase

# Publication of Risk Management Plan (RMP) Materials on the PMDA website

## 1. Introduction

It is important to use the Risk Management Plan (hereinafter, referred to as “RMP”) and the materials based on RMP in order to use drugs properly and to minimize the risks. 6 years have passed since RMP was introduced in 2013, and 467 RMP documents have been published on the Pharmaceuticals and Medical Devices Agency (hereinafter, referred to as “PMDA”) website at the end of August 2019. In addition, the materials prepared/provided as additional risk minimization activities of RMP (hereinafter, referred to as “RMP materials”) have been published on the PMDA website since April of this year.

This section will introduce the activities by MHLW/PMDA to facilitate the use of RMP and RMP materials for useful reference in clinical practice.

## 2. Definition of RMP

RMP is a document that integrates the risks of drugs (adverse reactions) collected through the “pre-approval” to “post-marketing” phases, and summarizes the information on what activity is to be performed to minimize the risks and what investigation is to be performed in order to obtain the missing information.

An MHLW guidance to establish RMP<sup>1)</sup> was issued in April 2012, and in accordance with this guidance, RMP has been prepared for new drugs and biosimilars/follow-on biologics for which approval applications were submitted on or after April 1, 2013. RMP has been prepared for generic drugs for which approval applications were submitted on or after August 26, 2014<sup>2)</sup>. In addition, RMP is also prepared/updated when safety concerns are newly found in the post-marketing phase of drugs or when otherwise an update is required. RMP is prepared by the Marketing Authorization Holder (MAH). Risks of drugs and the activities performed by MAH to minimize the risks are summarized in RMP, and the contents of RMP are verified by PMDA. Since RMP contains information on the potential risks that are not stated in the package inserts, it is important for healthcare professionals to understand the contents of RMP in addition to the contents of package inserts in order to facilitate the proper use of drugs and to minimize the risks.

## 3. Materials prepared/provided as part of additional risk minimization activities of RMP

### (1) Definition of additional risk minimization activities

The activities to mitigate/avoid risks are called risk minimization activities, such as seeking a way of providing the information on the risks and/or missing information written in RMP. The risk minimization activities are divided into the activities applied to all drugs (routine risk minimization activities) and the activities applied to certain drugs depending on their characteristics (additional risk minimization activities). Provision of information through package inserts and drug guides for patients is included in routine risk minimization activities. Meanwhile, establishment of conditions of the drug use and provision of materials for proper use are examples of additional risk minimization activities. The examples of RMP materials are the material for patients that explain subjective symptoms of adverse reactions in plain language and the materials for healthcare professionals that summarize necessary information for proper use of drugs. These RMP materials had their contents verified by PMDA during preparation, and have an “RMP mark” affixed on them to be distinguished from other materials prepared by MAHs<sup>3)</sup>. Healthcare professionals are encouraged to make the best use of RMP materials with an “RMP mark” affixed.

(2) How to obtain RMP materials (available only in Japanese including RMP documents and materials)

Among RMP materials, those that can be prepared as PDF files have been published on the PMDA website since April, 2019, and all RMP materials have been available on that website since September, 2019<sup>4)</sup>.

There are 2 ways to browse on the PMDA website: To find RMP materials in the list of RMP-submitted products [Left], or search by drug names on the page of package insert search [Right] (Figure 1).

From PMDA top page (<https://www.pmda.go.jp/>)

[Left] Safety Information/Recall Information → Risk Management Plan (RMP)

→ Click on Package Inserts/RMP Materials, etc. in the List of RMP-submitted Products

[Right] Find PI for Drugs → Search the package insert of the drug you would like to browse

→ Click the non-proprietary name on the search result

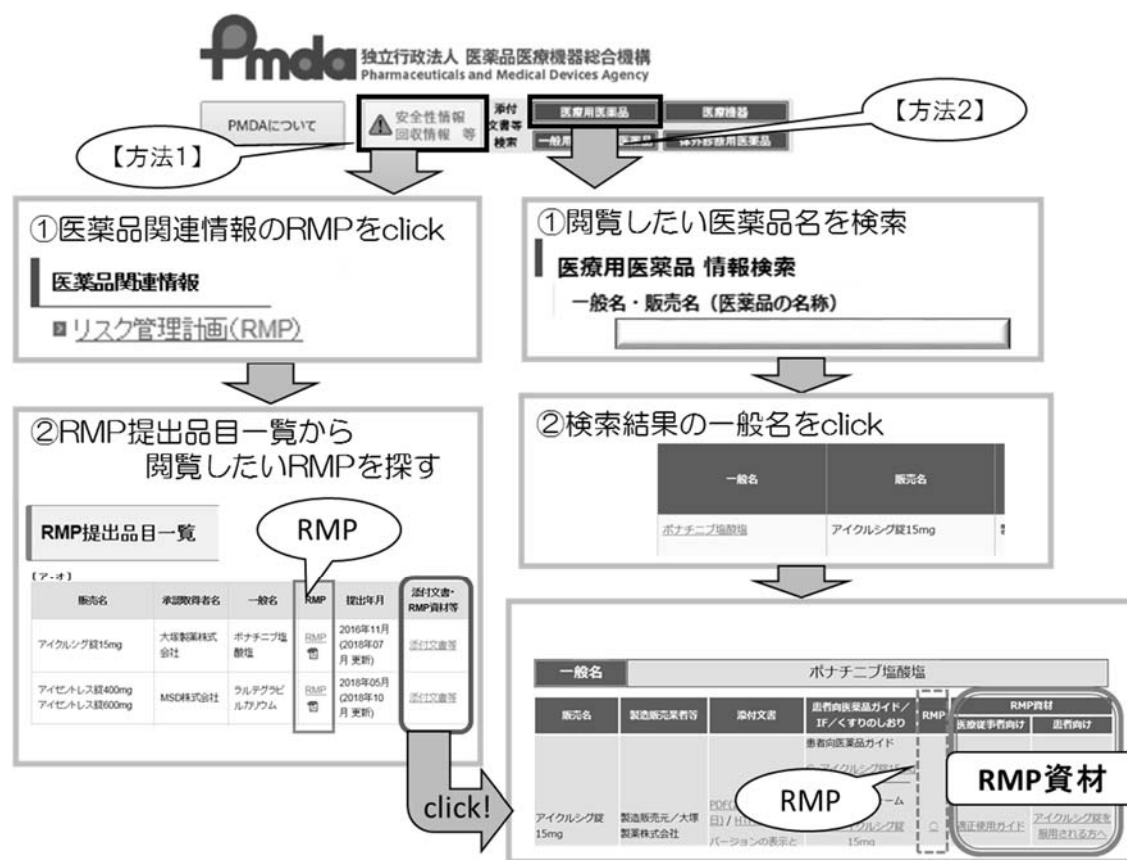


Figure 1: How to Browse RMP materials

## 4. For facilitation of the use of RMP

### (1) Background

As stated in the Pharmaceuticals and Medical Devices Safety Information No.358<sup>5)</sup>, according to the survey conducted by PMDA in the fiscal year (FY) 2017, the percentage of facilities that understood RMP was 48.2% in hospitals while the percentage was 17.4% in pharmacies. Among the facilities that understood RMP, the percentage of hospitals and pharmacies that had used RMP was as low as 50.6% and 39.4% respectively. Therefore, RMP and RMP materials have yet to be fully used.

In this section, activities for facilitating the use of RMP and RMP materials in medical practice will be introduced.

### (2) Information distribution by the PMDA Medi-navi

PMDA publishes RMP on the PMDA website, and delivers the information through the PMDA Medi-navi. In addition to newly prepared and published RMPs, since May 2019, PMDA has also delivered the information on the updated RMP for which an important update\* was made.

\* Creation or deletion of Safety Specifications, creation of additional risk minimization activities, other important changes

### (3) Learn about RMP in 3 Minutes!

In order to deepen the understanding of and to use RMP in healthcare professionals, PMDA prepared the document titled "Learn about RMP in 3 Minutes!" under the supervision of clinical practice specialists. This document explains the difference between RMP and package inserts, the contents of RMP, and the methods to obtain RMP and RMP materials, etc. in an easy-to-understand way using figures. In association with the recent start of RMP materials publication on the PMDA website, PMDA renewed the contents of this document for Version 2 (Figure 2).

This document can be downloaded from the PMDA website (Figure 3). Healthcare professionals are encouraged to use the information. This document can be supplied in print form for distribution in seminars, etc. Please feel free to contact us at the e-mail address below.

Note: "Learn about RMP in 3 Minutes!" is available in Japanese only.

Contact address for this document: [medinavi-ad@pmda.go.jp](mailto:medinavi-ad@pmda.go.jp)

Version 2

Learn about RMP in 3 Minutes!

To become a higher-level pharmacist! Understand and use the contents of Risk Management Plan (RMP)

Documentation: International Information Group, Risk Communication Promotion Division, Office of Information and Management for Safety, Pharmaceuticals and Medical Devices Agency  
 Cooperation: Japan Pharmaceutical Association  
 Supervision: Saitama Wakabayashi (Department of Pharmacy, Kyorin University Hospital)

**What's RMP??** 30sec

In order to minimize the risks of drugs (adverse reactions), it is necessary to provide the information on the risks found from the development phase and the regulatory review, and to check the missing information in the post-marketing phase. People who are involved in each phase need to understand why they are doing that activity to implement this risk management properly. Risk Management Plan (RMP) is a document that summarizes a whole risk management process of the "development," "regulatory review," and "post-marketing" phases. This document plays the role of a bridge that connects the risk management process in the "development to regulatory review" phases and that in the "post-marketing" phase.

From non-clinical to clinical studies -  
 Regulatory Review - Confirmation of efficacy/safety on documents -  
 Post-Marketing - Actual use in patients -  
 Use RMP through a whole risk management process!

**What's the difference between package inserts and RMP??** 60sec

Since the number of cases is limited in clinical studies, a causal relationship with drug use is confirmed for some risks, while a causal relationship is suspected but not sufficiently confirmed for other risks. In addition, sufficient information is not provided under some study conditions due to the small number of cases such as elderly patients and infants.

Both package inserts and RMP contain risk information, but the types of risks written in these documents are different as shown in the figure. One of the characteristics of RMP is that it contains not only identified risks but also potential risks and missing information.

Package Inserts	RMP
<ul style="list-style-type: none"> <li>Adverse reactions confirmed during clinical studies or the post-marketing phase</li> <li>Serious adverse reactions, other adverse reactions</li> <li>Important identified risks</li> </ul>	<ul style="list-style-type: none"> <li>Adverse reactions not fully confirmed through their association with drugs is suspected</li> <li>Important potential risks</li> <li>Insufficient information under some study conditions such as elderly patients and infants</li> <li>Important missing information</li> </ul>

**What's written in RMP??** 90sec

The 3 risks described in RMP (important identified risks, important potential risks, important missing information) are collectively called the "safety specifications." For these safety specifications, RMP gives information on how to "gather information" and how to "provide information." In RMP, the activities for "information gathering" are called "Pharmacovigilance Activities" and the activities to "mitigate/avoid risks" such as "information provision" are called "Risk Minimization Activities."

These activities are divided into 2 types: Activities performed for all drugs (routine activities) and activities performed depending on the characteristics of drugs (additional activities).

Pharmacovigilance Activities (Information Gathering)	Risk Minimization Activities (Information Provision)
<ul style="list-style-type: none"> <li>Routine activities</li> <li>Collection of adverse reaction cases</li> <li>Additional activities</li> <li>e.g.) Collection of information through early post-marketing phase vigilance, use of the survey, and post-marketing clinical study</li> </ul>	<ul style="list-style-type: none"> <li>Routine activities</li> <li>Preparation and provision of package insert drug guides for patients</li> <li>Additional activities</li> <li>e.g.) Provision of information based on early post-marketing phase vigilance, distribution of materials for proper use, and establishment of conditions of the drug use</li> </ul>

**Where can I browse RMP??** 20sec

2 browsing methods are available!

All of the prepared RMPs are published on the PMDA website. You can access RMP by 2 methods. (Method 1) access the List of RMP Submitted Products\* and find the RMP you want to browse from the list, or (Method 2) search individual drugs on the page of package insert search to browse RMP of the drugs. When a new RMP is published or an important change\* was made, the information is delivered through the PMDA Medi-navi.

\*RMP reviewing methods are available in Japanese only including RMP documents and materials.  
 \*e.g. Creation or deletion of safety specifications, creation of additional risk minimization activities and other important changes

You can browse RMP materials (for healthcare professionals, and for patients) on this page.

**Do you know the RMP mark??** Break time

Materials prepared as a part of additional risk minimization activities of RMP (information provision) have a mark shown on the right. The necessity and contents of these materials were verified by PMDA during regulatory review, etc. Please use these materials when selecting materials for medication guidance.

Reference: Marking on Materials Prepared and Distributed for Additional Risk Minimization Activities in Risk Management Plan (RMP) (Administrative Notice dated June 8, 2017)

**Make the best use of RMP!** 150sec

- Start with browsing through the RMP Outline Sheet! Understand what risks are assumed, what investigation is performed, and what material is prepared.
- Check RMP when using a new drug! Use RMP to understand the risks of newly introduced drugs (e.g., new drugs). Use "important identified risks" for the monitoring of patients!
- Use the information on important identified risks in monitoring adverse reactions efficiently (e.g., setting identified risks as monitoring items).
- Check potential risks when investigating causing agents for adverse reactions!
- RMP contains the information on potential risks that have yet to be listed in package inserts. Checking RMP is an option when you encounter an adverse reaction that is not stated in the package insert during the investigation of the causing agent.
- Use "the materials for healthcare professionals" and "the materials for patients" that are designated as the materials of additional risk minimization activities!
- Use the risk minimization materials listed in RMP. Please also check the above RMP mark. These materials are now available on the PMDA website.

\* Please refer to the recommendations on the use of RMP stated in the Use of Risk Management Plan of Drugs in Clinical Practice of Hospital Pharmacists, dated December 15, 2014 (Japanese Society of Hospital Pharmacists).

Everyone, please make the best use of RMP!

3min!!

Figure 2: Learn about RMP in 3 Minutes! (Version 2)

**RMP提出品目一覧**

医療従事者の皆様へのお断り

RMPをご案内いただくことで、それぞれの医薬品に、現時点でどのような重要な安全性の懸念(安全性検討事項)があるのか、また、安全対策として製造販売業者が医療現場にお断りしていることや協力をお断りしている市販法の調査や臨床試験が、どのような目的で実施されているのかの理解に役立てて頂ければ幸いです。RMPにおいて実施が予定されている調査や臨床試験は、その結果を医薬品の適正使用に活用して頂くために不可欠なものです。皆様のご理解とご協力をよろしくお願い申し上げます。

**RMPについてわかりやすく解説した資料「3分でわかる！RMP講座」はこちら**

**RMPとは**

医薬品の安全性の確保のためには、開発の段階から市販後に至るまで常にリスクを適正に管理する方策を講ずることが必要です。RMPは、この開発から市販後まで一貫したリスク管理の取組みの連携に合わせた取り組みを公表して、医療関係者の皆様との連携強化を図ることが期待されています。

**②「3分でわかる！RMP講座」はこちらをクリック**

なお、RMPについてわかりやすく解説した資料を以下に掲載しています。ダウンロードの上、ぜひご利用ください。

**3分でわかる！RMP講座**

本資料に関するお問い合わせ先: medinavi-ad@pmda.go.jp  
 ※ 迷惑メール防止対策をしているため、\*を半角の

**3分でわかる！RMP講座やRMPに関する過去のPMDSIなどが閲覧できます**

**医薬品関連情報**

- 緊急安全性情報・安全性情報
- 医薬品の適正使用法に関するお知らせ
- 医薬品・医療機器に関するお知らせ
- 医薬品に関するお知らせ
- 使用上の注意
- PMDA医療安全情報
- 回収情報
- 副作用が疑われる事例報告に関する情報
- コゼネン系医薬品の不具合が疑われる症例情報
- リスク管理計画(RMP)**

① 医薬品関連情報の医薬品リスク管理計画(RMP)をクリック

Figure 3: How to download "Learn about RMP in 3 Minutes!"

## 5. Closing Comments

Drugs are approved with limited data from clinical studies and other sources, and their efficacy and safety are ensured with accumulating use experience in the post-marketing phase. Healthcare professionals are expected to understand “why this investigation is performed” or “why this material is prepared” by using RMP in medical practice, and to join the drug risk minimization activities. PMDA encourages healthcare professionals to deepen their understanding of RMP by using “Learn about RMP in 3 Minutes!” introduced this time and to make the best use of RMP and RMP materials.

Other than RMP and RMP materials, various tools such as drug guides for patients and manuals for management of individual serious adverse drug reactions are published on the PMDA website. Please use these tools in addition to RMP to ensure the safety of drugs such as when giving drug administration guidance for patients.

## 6. References

- 1) Risk Management Plan Guidance for Drugs (Joint PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No.0411-2, by the Director of Safety Division and the Director of Evaluation and Licensing Division, Pharmaceuticals and Food Safety Bureau, MHLW dated April 11, 2012)  
<https://www.pmda.go.jp/files/000145482.pdf> (only in Japanese)
- 2) Application of the Risk Management Plan Guidance for Drugs to Generic Drugs (Joint PFSB/ELD Notification No.0826-3 and PFSB/SD Notification No. 0826-1, by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceuticals and Food Safety Bureau, MHLW dated August 26, 2014)  
<https://www.pmda.go.jp/files/000145421.pdf> (only in Japanese)
- 3) Marking on Materials Prepared and Distributed for Additional Risk Minimization Activities in Risk Management Plan (RMP) (Administrative Notice dated June 8, 2017)  
<https://www.pmda.go.jp/files/000218503.pdf> (only in Japanese)
- 4) Partial Revision of the Publication of Drug Risk Management Plan (Joint PSEHB/ELD Notification No. 1029-1 and PSEHB/PSD Notification No. 1029-1 by the Director of Evaluation and Licensing Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated October 29, 2018)  
<https://www.pmda.go.jp/files/000226448.pdf> (only in Japanese)
- 5) Results of a Survey Investigating Access, Communication, and Utilization of Drug Safety Information at Hospitals and Pharmacies and Desirable Directions (Pharmaceuticals and Medical Devices Safety Information No. 358, issued in November 2018)  
<https://www.pmda.go.jp/files/000226850.pdf>



## 2

# 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) (hereafter, “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 pharmaceuticals despite using such products properly. This is a public service funded by contributions from marketing authorization holders (MAHs) of pharmaceuticals 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 is now being covered by the Relief System since November 25, 2014.

In this Relief System, a total of 23 026 cases have been granted relief benefits since the establishment of the Relief System in 1980 until the end of fiscal year 2018.

### 2. Awareness of Relief System for Adverse Drug Reactions<sup>Note 1)</sup>

Awareness of the Relief System among the general public in FY2018 was 29.7% in total: 8.9% 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 83.7% in total: 62.6% answered that they “were aware” of the Relief System and 21.1% answered that they “have heard about” the Relief System. By occupational category, awareness was 92.3% among physicians, 98.3% among pharmacists, 60.5% among nurses, and 83.8% 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 8.8% in total: 9.1% among physicians, 10.8% among pharmacists, 6.8% among nurses, and 6.6% among dentists. Furthermore, in all application forms related to relief benefits, the field for “the source of information related to the Relief System” (select from “Physician,” “Dentist,” “Pharmacist,” “Other medical facility staff,” “Newspaper/TV, etc.” and “Others”) was included in April 2016 to understand the sources of information related to the Relief System. The FY2018 results showed “Physician” in 444 answers (30.5%), “Others” (the Internet) in 245 answers (16.8%), “Newspaper/TV etc.” in 140 answers (9.6%) and “Pharmacist” in 136 answers (9.3%) in descending order (multiple answers acceptable)<sup>Note 2)</sup>.

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 utilize 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.

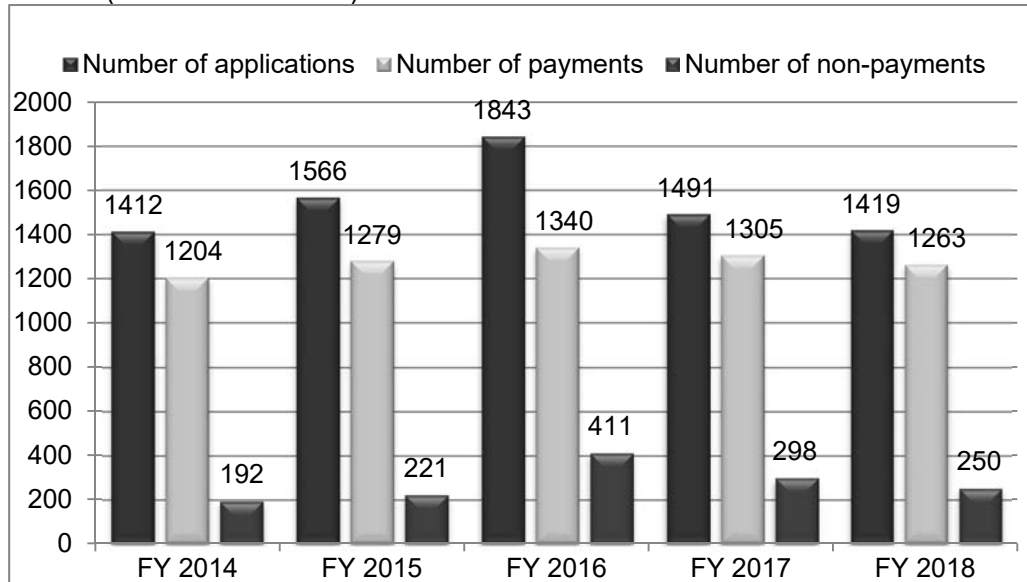
### 3. Status of payment/non-payment cases in the Relief System

The annual numbers of applications and payments in the Relief System between FY 2014 and FY 2018 are shown in Figure 1. In FY2018, the number of applications was 1 419, the number of payments was 1 263, and the number of non-payments was 250. The percentage of payments/non-

payments and the breakdown of reasons for non-payments from FY2016 to 2018 are shown in Figure 2.

In addition, the goal of standard administrative processing time <sup>Note 3)</sup> from when PMDA receives an application to when PMDA notifies the applicant of the decision was within 6 months in 60% or more of cases for which payment or non-payment was determined. The actual achievement percentage in FY2018 was 65.7%.

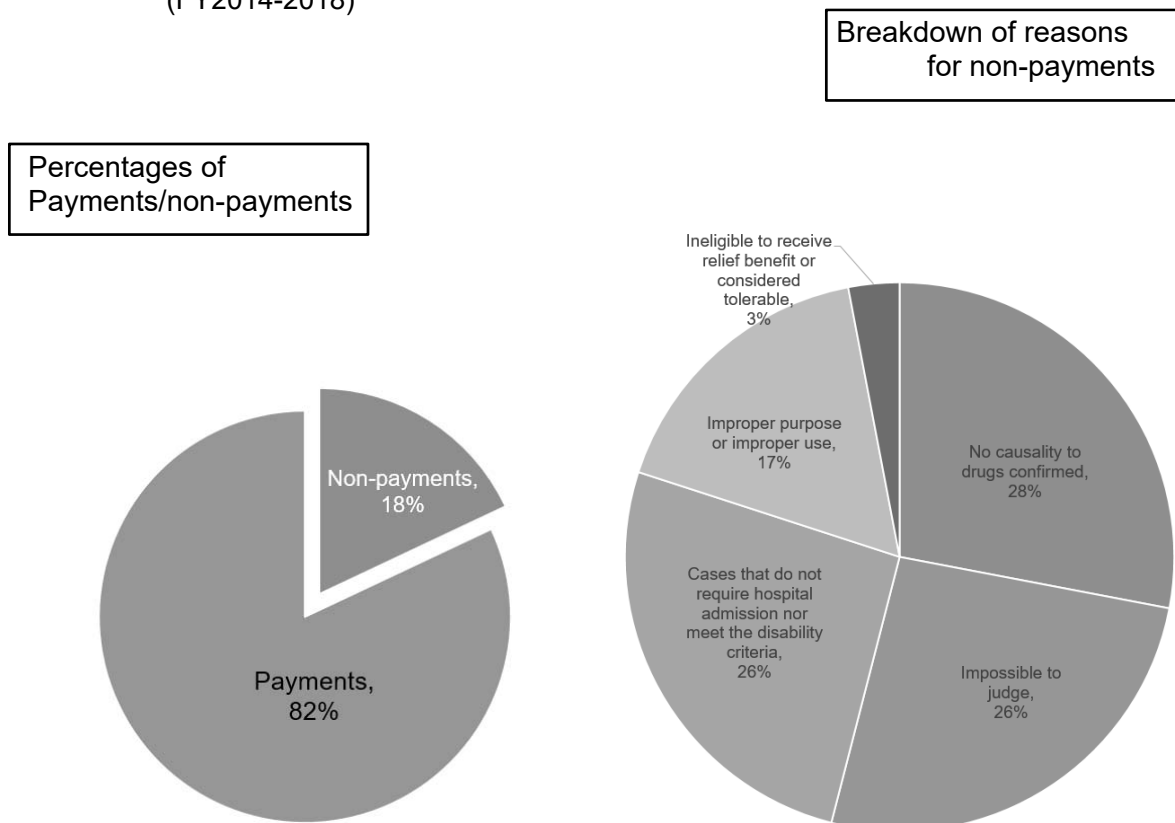
Figure 1 Number of payments and non-payments under the Relief System for Adverse Drug Reactions (FY2014 to FY2018)



(Explanation of the figure)

- \* The number of cases is based on the number of applicants. Therefore, if an applicant submits another claim for the same cause after the applicant's first claim for a cause was submitted, the 2 applications are counted as 1 case.
- \* The number of applications and total number of payments and non-payments made within an FY are not consistent since a certain period is required from receipt of an application to the decision on benefit payments.

Figure 2 Percentages of payments/non-payments and breakdown of reasons for non-payments (FY2014-2018)



#### 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 pharmaceuticals or regenerative medical products (hereafter, “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>).

[Types and amounts of relief benefits (as of April 1, 2019)]

Medical Expenses (costs borne by the patients, not including health insurance payments)

- Actual costs of treatment for disease caused by ADRs will be compensated. (34 800 JPY to 36 800 JPY per month)
- Benefits are provided for costs other than medical costs for treatment of diseases caused by ADRs.

Disability Pensions (Grade 1: Annually 2 796 000 JPY, Grade 2: Annually 2 236 800 JPY)

- Benefits are provided to compensate for living costs, etc. of patients aged 18 and older, who suffer from a certain degree of disability due to adverse reactions.

Pensions for Raising Children with disabilities (Grade 1: Annually 873 600 JPY, Grade 2: Annually 699 600 JPY)

- 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 Pensions (2 444 400 JPY)

- Benefits are provided for bereaved families to rebuild their lives following the death of their main provider from ADRs.

Lump-Sum Benefits for Bereaved Family (7 333 200 JPY)

- Benefits are provided for bereaved families for condolence and sympathy following the death

of a family member who is not the main provider from ADRs.

Funeral Expenses (206 000 JPY)

- Benefits are provided to cover the cost of holding a funeral for people who died of ADRs.

[Cases of relief benefit payments]

<Case 1> A case where medical expenses/medical allowances were provided for the occurrence of erythema multiforme type drug eruption due to salazosulfapyridine

A female in her forties. Erythema multiforme type drug eruption occurred after administration of Azulfidine EN Tablets (salazosulfapyridine), and the patient was admitted to hospital for treatment. Medical expenses/medical allowances were provided.

<Case 2> A case where medical expenses/medical allowances/lump-sum benefits for bereaved family/funeral expenses were provided for sigmoid colon perforation due to a contrast medium

A female in her sixties. Sigmoid colon perforation occurred after the use of Barium Sulfate Powder (barium sulfate) at a medical examination and the patient was admitted to hospital for treatment. The patient died due to secondary peritonitis, and medical expenses/medical allowances/lump-sum benefits for bereaved family/funeral expenses were provided.

<Case 3> A case where disability pensions were provided for a disability caused by optic atrophy due to voriconazole

A male in his thirties. Optic atrophy occurred after the use of VFEND Tablets (voriconazole) that resulted in visual impairment, and disability pensions were provided.

<Case 4> A case where medical expenses/medical allowances were provided for drug-induced liver injury due to an over-the-counter drug

A female in her twenties. The patient was admitted to the hospital for treatment due to drug-induced liver injury after the use of Cought Granules. Medical expenses/medical allowances were provided.

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

Of the 1 372 non-payment cases from FY2014 to FY2018<sup>Note4)</sup>, approximately 17% of them were due to the proper purpose or method of use of the pharmaceutical not being able to be confirmed (Figure 2). The most recent (approximately the last year) reasons why the method of use was not considered proper are presented in this section together with the description provided in the package inserts or specific cases. Table 1 shows the most common pharmaceuticals for which the method of use was not considered proper.

Table 1 Number of cases where the drug was not used for the proper purposes (2014-2018)

Name of causative drug	FY2014	FY2015	FY2016	FY2017	FY2018	Total (cases)
Lamotrigine	24	23	24	9	12	92
Thiamazole	2	5	3	1	3	14
Lithium carbonate	0	1	8	0	1	10
Methotrexate	2	2	0	1	1	6
Carbamazepine	2	0	0	1	2	5
Other	25	23	19	16	25	108
Total (cases)	55	54	54	28	44	235

### (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 are required to reconfirm the package insert and to use the drug considering its dosage and administration.

**<Case> A case of drug-induced hypersensitivity syndrome due to lamotrigine**

A male in his forties. In a prescription of Lamictal Tablets (lamotrigine) used for bipolar affective disorder without sodium valproate, and with drugs other than those inducing glucuronidation, the drug was started from a daily dose of 50 mg, which was increased to 100 mg/day after 7 days, to 150 mg/day after 14 days, and to 200 mg/day after 21 days of administration. 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<sup>Note 5)</sup> 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.

Many of these cases in which 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 pharmaceuticals. Please make sure to read the package insert carefully before use.

Figure 3 shows examples of dosage and administration when used for suppression of recurrent/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

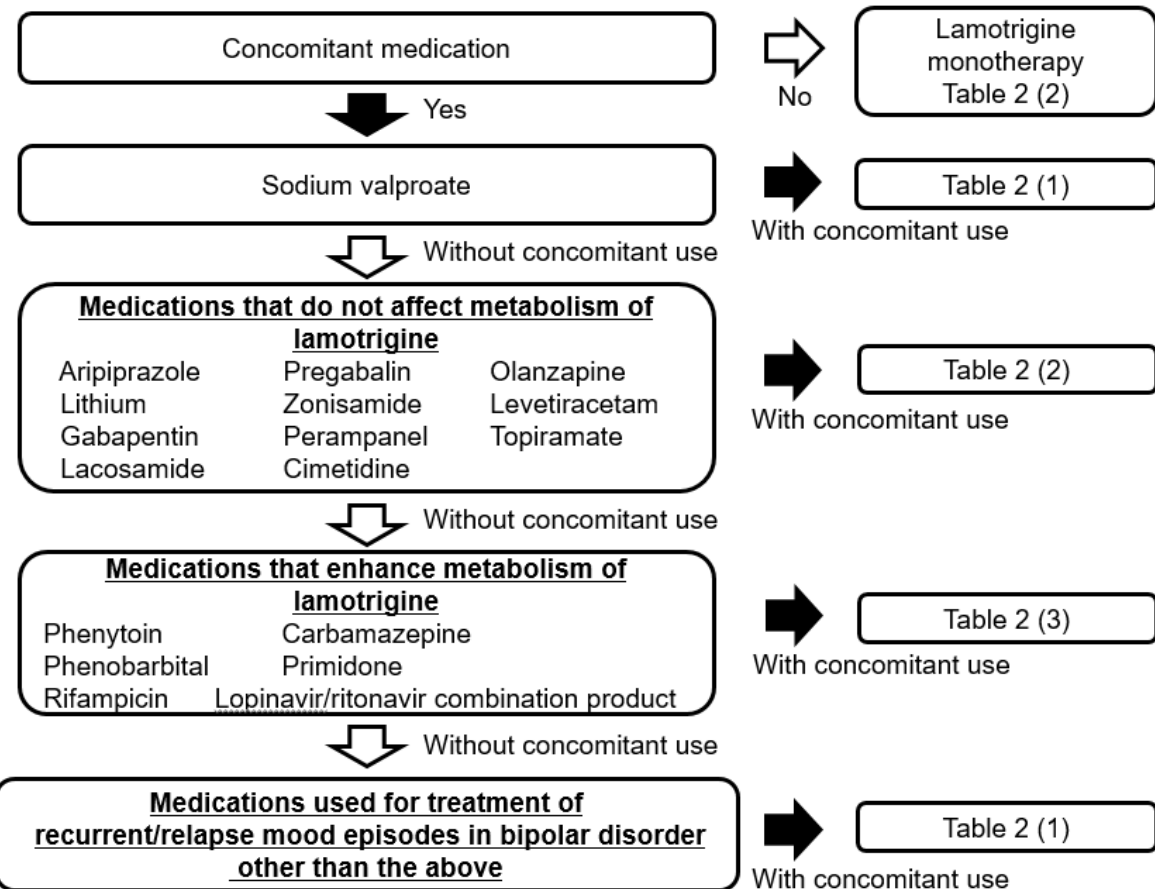


Table 2 Starting dose of lamotrigine

	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 pharmaceuticals 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 female in her forties. Since no blood test including differential count of leukocytes had been conducted for 40 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, 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 hypercalcaemia and secondary acute kidney injury due to eldecalcitol

A female in her eighties. Since the prescription of Ediol Capsules (eldecalcitol) was taken over from her previous physician, the drug was continuously administered even after decreased renal function was observed approximately 5 months later and serum calcium level had never been measured within the subsequent 2 months until it was found to be high. Thus, the case was not approved as proper use.

#### Description in the package insert of Ediol Capsules (Partial excerpt)

##### Important Precautions

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

When symptoms related to hypercalcaemia (malaise, irritability, queasy, thirst, decreased appetite, depressed level of consciousness, etc.) occurred, the patient should be monitored carefully through means including measurement of serum calcium.

##### Clinically Significant Adverse Reactions

Acute renal failure (frequency unknown): Acute renal failure associated with increased serum calcium may occur. Serum calcium and renal function should be monitored periodically. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

## (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 patient 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 and ascites retention

A female in her seventies. Although there were suspected ascites retention based on abdominal echography and hepatic cirrhosis based on abdominal CT scan approximately 10 years after the start of treatment with methotrexate products, methotrexate was continuously used even after that

for over 2 months. Since methotrexate is contraindicated for “patients with chronic liver disease” and “patients with pleural effusion, ascites, etc.,” the use was not considered proper.

**Description in the package insert of methotrexate (Partial excerpt)**

CONTRAINDICATIONS (Methotrexate should not be administered to the following patients)

- 4) Patients with chronic liver diseases [Adverse reactions may be more severe.]
- 7) Patients with pleural effusion, ascites, etc. [Toxicity of methotrexate may be more severe due to prolonged retention in pleural effusion, ascites, etc.]

**(4) Cases where patients used drugs at their own discretion 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 use 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 acute renal failure due to loxoprofen sodium hydrate**

A male in his sixties. Since the patient took the residual Loxonin Tablets (loxoprofen sodium hydrate) that were previously prescribed by a physician at his own discretion, this case was not considered proper.

**<Case 2> A case of drug-induced hypersensitivity syndrome (DIHS) due to carbamazepine**

A female in her sixties. Although discontinuation of Tegretol Tablets (carbamazepine) was instructed by the occurrence of cutaneous symptoms, the patient continued its use at her own discretion until emergency hospitalization became necessary due to extended cutaneous symptoms all over the body. Therefore, this drug use was not considered proper.

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

Among the cases where patients were administered drugs to which they had a history of adverse reactions by physicians who knew the history, uses sometimes 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 oculomucocutaneous syndrome (Stevens-Johnson syndrome) due to levofloxacin**

A female in her seventies. Although there was a description about a history of skin eruption (history of allergy) due to levofloxacin in her medical record, Levofloxacin Tablets (levofloxacin) was prescribed for cystitis without confirming the details of the record; therefore, 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/adr-sufferers/0001.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 responsible for payment of damages such as MAHs <sup>Note 6)</sup>
- C. Cases of adverse health effects as a result of using the pharmaceutical 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 <sup>Note 7)</sup>
- D. Cases in which the purpose/method of use is not confirmed to be proper (such as cases in which pharmaceuticals are used in other ways than the indications approved by the Minister of Health, Labour and Welfare, or cases in which pharmaceuticals 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  
Pharmaceuticals not considered eligible include <sup>Note 8)</sup>:
  - i Pharmaceuticals used for the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
  - ii Pharmaceuticals that do not have the possibility to cause ADRs, including pharmaceuticals not used directly on human bodies or pharmaceuticals 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 pharmaceuticals fail to meet the disability criteria under the Relief System <sup>Note 9)</sup>
- 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 pharmaceuticals 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 healthcare professionals are consulted by their patients about ADRs, healthcare professionals should provide information on the Relief System to the patient or family members 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 (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](mailto:kyufu@pmda.go.jp)

Note 1) From: 2018 Awareness Survey on the Relief System for Adverse Drug Reaction (only in Japanese)

<http://www.pmda.go.jp/relief-services/adr-sufferers/0023.html>

Note 2) Annual Report FY 2018 (Pharmaceuticals and Medical Devices Agency)

<https://www.pmda.go.jp/files/000230686.pdf> (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 based on the number of applicants. Therefore, if an applicant submits another claim for the same cause after the applicant's first claim for a cause was submitted, 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) "Person responsible for payment of damages" typically refers to the person in charge, etc. for accidents due to adulterated drugs such as mutated drugs or contaminated drugs."

Note 7) 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 pharmaceutical is used in critical care situations.
- (2) There are no alternative treatment modalities available.
- (3) A higher dose of the pharmaceutical 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 8) Drugs not eligible for relief benefits

<https://www.pmda.go.jp/relief-services/adr-sufferers/0044.html> (only in Japanese)

Note 9) Degree of disability does not meet the criteria of "Disability that prevents a person from performing daily life activities by himself/herself (Grade 1)" or "Disability that results in significant limitations during the patient's daily life activities (Grade 2)"

# Efforts for 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 2019, there have been 313 of the total 499 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 Vaccine Promotion such as for cervical cancer vaccines” <sup>Note)</sup> 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](http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/sesshu_youryou.pdf)

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. <sup>Note)</sup>

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	Total		
Number of claims	334 cases	141 cases	86 cases	796 cases		
Number of Payments	314 cases	223 cases	111 cases	749 cases		

(Source: Annual Report FY 2018)

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

### 3. 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 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](http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/madoguchi/dl/151116_02.pdf) (only in Japanese)

Administrative notice issued by the Safety division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated October 22, 2015 (Request for) 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”

<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 (Request for) Relief Benefits for Adverse Health Effects due to “Urgent Vaccination Promotion such as for cervical cancer vaccines”

<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)

# 3

## Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated September 24, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

### 1 Baricitinib

<b>Branded name (name of company)</b>	Olumiant tablets 2 mg, 4 mg (Eli Lilly Japan K.K.)
<b>Therapeutic category</b>	Miscellaneous metabolism agents-miscellaneous
<b>Indications</b>	Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage)

#### PRECAUTIONS (revised language is underlined)

[Under New instructions]

**8. IMPORTANT PRECAUTIONS** (deleted)

**11. ADVERSE REACTIONS** Venous thromboembolism  
Pulmonary embolism and deep vein thrombosis may occur.

(Clinically Significant Adverse Reactions)  
(newly added)

**Reference information**

Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 22-month period (September 2017 to June 2019)  
Cases involving venous thromboembolism: 1 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 000

Japanese market launch: September 2017

## Case summary

No.	Patient		Daily dose and administration duration	Adverse reaction
	Sex/ age	Indication for use (Complication)		Clinical course and treatment provided
1	Female In her seventies	Rheumatoid arthritis (Cervical spondylosis, unruptured aneurysm, hyperlipidaemia)	2 mg 209 days ↓ Discontinuation	<p>Venous thromboembolism Pulmonary embolism Medical history: History of thrombosis, varicose vein, or venous thromboembolism was absent. The patient had no problem with daily living activities and had a very active personality. Previous use of biological agents and JAK inhibitors: golimumab, tofacitinib Disease duration: 2 years</p> <p>Day 1 of administration Administration of baricitinib was started for rheumatoid arthritis (Stage II, Class II) at a dose of 2 mg/day.</p> <p>Day 170 of administration Swelling of the right foot developed. There was no other symptom in particular.</p> <p>Day 175 of administration (Date of onset) Vital sign: Blood pressure, 111/52 mmHg; pulse, 71/min; SpO2, 98% (room air); body temperature, 37 degrees C. There was no symptom of dehydration. Blood test: The table below should be referred to. Blood vessel echo was performed, and it showed thrombus in the right femoral vein. Contrast enhanced CT: There was no poorly contrasted area suggestive of thrombus or no shadow suggestive of pulmonary embolism in the pulmonary artery. There was poorly contrasted area from the right posterior tibial vein and popliteal vein to femoral vein. Oedematous swelling was present in the subcutaneous region of the right lower thigh. Venous thromboembolism was diagnosed (pulmonary embolism was absent). The patient was admitted to start to receive treatment with rivaroxaban (Administration of this drug has been continued).</p> <p>Day 176 of administration Swelling of the right leg showed a resolving tendency.</p> <p>Day 182 of administration The patient was discharged since the events were determined to have resolved.</p> <p>Day 195 of administration The dose of rivaroxaban was reduced from 30 mg/day to 15 mg/day.</p>

			<p>Day 204 of administration</p> <p>Swelling and pain in the leg developed. Respiratory discomfort was absent. Vital sign: Blood pressure, 131/73 mmHg; pulse, 56/min; SpO2, 97%(room air); body temperature, 35 degrees C. There was no symptom of dehydration. Blood test: The table below should be referred to. Contrast enhanced CT: Thrombi were observed in the area from superficial femoral vein to the fibular veins and the lower lobe of the right pulmonary artery. Recurrence of venous thromboembolism and pulmonary embolism were diagnosed. The patient was admitted. Treatment with apixaban was started.</p> <p>Day 209 of administration (day of discontinuation)</p> <p>Administration of baricitinib was discontinued.</p> <p>12 days after discontinuation</p> <p>The events resolved, and the patient was discharged.</p>
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Laboratory test values

	Day 126 of administration	Day 175 of administration (Date of onset)	Day 203 of administration	Day 204 of administration
White blood cell (μL)	4 700	5 400	4 100	4 500
Hb (g/dL)	10.4	10.2	9.8	10.3
Platelets (×103/μL)	234.0	148.0	196.0	220.0
AST (U/L)	20	25	33	27
ALT (U/L)	18	19	34	28
Creatinine (mg/dL)	0.93	1.10	1.01	1.06
BUN (mg/dL)	15	21	19	19
Na (mmol/L)	144	143	143	143
K (mmol/L)	4.7	4.5	4.4	3.9
Cl (mmol/L)	113	114	111	112
CRP (mg/dL)	0.08	0.12	0.04	0.03
D-dimer (μg/mL)	-	17.98	-	1.52

-:Not measured

Concomitant drugs: prednisolone (5 mg/day), methotrexate (6 mg/week), iguratimod (50 mg/day), denosumab, alfacalcidol, folic acid, lansoprazole, mecobalamin, clonazepam, and pravastatin sodium



## 2 Osimertinib mesilate

<b>Branded name (name of company)</b>	Tagrisso Tablets 40 mg, 80 mg (AstraZeneca K.K.)
<b>Therapeutic category</b>	Antineoplastics-miscellaneous
<b>Indications</b>	<i>EGFR</i> gene mutation-positive inoperable or recurrent non-small cell lung cancer

### PRECAUTIONS (revised language is underlined)

#### [Under Old instructions]

#### Adverse Reactions

#### (Clinically Significant

#### Adverse Reactions)

#### (newly added)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome, and erythema multiforme may occur. Patients should be carefully monitored and appropriate measures should be taken such as discontinuing this drug if any abnormalities are observed.

#### [Under New instructions]

#### 11. ADVERSE REACTIONS

#### (Clinically Significant Adverse Reactions)

#### (newly added)

#### Reference information

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme

Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 38-month period (May 2016 to June 2019)

Cases of toxic epidermal necrolysis: 0

Cases of oculomucocutaneous syndrome: 2 (no patient mortalities)

Cases involving erythema multiforme: 3 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 11 000

Japanese market launch: May 2016

## Case summary

№	Patient		Daily dose Administra- tion duration	Adverse reaction	
	Sex/ Age	Indication for use (Complication)		Clinical course and treatment provided	
1	Female In her eighties	Non-small cell lung cancer (None)	80 mg 45 days	<p><b>Stevens-Johnson syndrome</b> Medical history: Dyslipidaemia, chronic gastritis, diabetes mellitus. Other: Non-smoker</p> <p>Day 1 of admin- istration      Administration of this drug was started at a dose of 80 mg/day.</p> <p>Day 32 of admin- istration      At outpatient visit, rash around the fingernails was noted.</p> <p>Day 42 of admin- istration      Skin eruption with itching appeared in the area from the face to the neck. It gradually extended from the body trunk to the thigh.</p> <p>Day 45 of admin- istration      The last dose of osimertinib mesilate (day of discontinu- ation)      was administered.</p> <p>1 day after discon- tinuation      The patient made an outpatient visit. A sample for histological examination was obtained, and incisional biopsy (skin) was performed. Lidocaine injec- tion 1% E 3mL and chlorhexidine glu- conate 0.1% solution were adminis- tered.</p> <p>Toxicoderma that had developed 4 days earlier was suspected. Erythema was prominent on the body trunk and the extremities (area from the scalp to the face, the neck to the body trunk, the upper arm, and the thigh). Ery- thema on the body trunk showed a tendency to fuse with each other. Itch- ing was severe. Mild bulbar conjunc- tiva hyperaemia was noted. Admin- istration of osimertinib mesilate, which was one of the suspected drugs, was withdrawn.</p> <p>A possibility of drug-induced skin erup- tion could not be ruled out, and the skin eruption was monitored while be- ing managed on an inpatient basis.</p> <p>A Fexofenadine tablet 60 mg, twice daily after breakfast and dinner was prescribed for 3 days. The tablet was administered in the afternoon and be- fore sleep on that day. The patient was treated with 3 tubes of diflora- sone diacetate ointment 0.05% (5 g/tube) and application of white petro- latum 15g (2 times/day, on the body). 2 bottles of betamethasone butyrate propionate 0.05% lotion 10 g were applied (2 times/day, on the scalp).</p>	

				<p>2 days after discontinuation</p> <p>3 days after discontinuation</p> <p>5 days after discontinuation</p>	<p>The patient presented to the department of ophthalmology for hyperaemia in both eyes. Conjunctivitis was diagnosed. Skin eruption on the face had slightly increased. Keratoconjunctive erosion was absent. Only mild conjunctival hyperaemia was noted. Eye drops were prescribed (levofloxacin hydrate ophthalmic solution 1.5%+ fluorometholone ophthalmic solution 0.1%, both eyes, 3 times, daily) (until 9 days after discontinuation).</p> <p>Erythema on the thoracoabdominal region showed a tendency to fuse. Lip erosion was absent. Administration of lansoprazole was discontinued. Other concomitant drugs the patients had been receiving from prior to the admission were continued (betahistine mesilate, menatrenone bezafibrate).</p> <p>The patient visited the department of ophthalmology. The eye lesion had not progressed. There was no change in distress in the patient. The patient seemed to scratch her body during the night. The color tone of skin eruption on the upper back seemed to have faded, but erythema on both upper arms was accompanied by blister. Skin eruption on the extremities increased. Systemic administration of prednisolone 30 mg/day was started. Topical administration of steroid was still continued.</p> <p>Blister and erosion were present on the face or other regions, but the proportion of the area affected by erosion to body surface area was 10% or lower, general condition was good and enanthema was not severe. As a result of examination, intravenous immunoglobulin preparation (IVIg) therapy was started according to treatment policy for Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) based on disease activity evaluation for SJS or TEN since treatment response to prednisolone was inadequate.</p> <p>Oral medications that had been used before admission were discontinued just in case, although the possibility of contribution of these drugs was considered unlikely.</p>
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				<p>9 days after discontinuation</p> <p>10 days after discontinuation</p>	<p>The patient had pyrexia, but had no distress. Itching on the back started to disappear. Skin eruption on the body trunk and the extremities showed a tendency to fade, but blister and erosion on the face had partially extended. Palpebral conjunctival hyperaemia was absent. The body temperature was between 37 and 38 degrees C.</p> <p>Topical treatment was provided for erosion on the face on an outpatient basis. Prednisolone valerate acetate was applied, and then covering/protective dressings for thermal burn (surgical covering/ protective dressings) were provided. Non-adhesive covering/ protective dressings for wound were provided on the erosion on the cheek, followed by protection with bandages and net. Covering/ protective dressings for thermal burn (surgical covering/ protective dressings) and gauze were provided on erosion on the right abdominal region. Review was performed in a pathological conference. Histopathological examination showed epidermal necrosis. Extended erythema and pyrexia were clinically observed. Area affected by epidermolysis did not reach 10% of the body surface area as a result of the treatment. Treatment was provided as SJS.</p> <p>Treatment with intravenous immunoglobulin preparation (freeze-dried polyethylene glycol-treated human immunoglobulin) 15 g, once daily was started (until 14 days after the administration discontinuation).</p> <p>The color tone of erythema on the body trunk and the extremities had faded, but new development of pustule was noted on the breast and right upper arm, and thus punch biopsy was performed and the sample obtained was submitted for culture. There was no lesion in the genital area. The body temperature was 36.9 degrees C.</p> <p>Food intake was good without aggravation of general condition. Topical treatment was provided on an outpatient basis.</p> <p>Simple application of diflorasone diacetate as a mixture was performed to skin eruption on the body trunk and the extremities. Dimethylisopropylazulene was applied to erosion on the face and the upper arm, and then covering/ protective dressings for thermal burn (surgical covering/ protective dressings) was provided, followed by protection with bandages/gauze and net.</p>
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				11 days after discontinuation	Erosion on the face started to dry on the same day. There was no aggravation of redness around the erosion, no palpebral conjunctival hyperaemia, no extension of erosion on the abdominal region and upper extremities was observed.
				12 days after discontinuation	Erosion on the face and upper extremities showed a tendency toward epithelization. Erythema showed a tendency to fade. No new development of blister or pustule. Palpebral conjunctival hyperaemia was absent. The body temperature was 37.2 degrees C. Blood culture: Negative. Pus in the skin: <i>Staphylococcus (Staphylococcus species)</i> .
				15 days after discontinuation	Itching had almost disappeared. Tingling sensation on the cheek disappeared. There was epithelization of erosion on the face, the right upper extremity, and the body trunk, while erosion on the left upper extremity remained with shallow ulcers in some parts, and fading of erythema had progressed. IVIg therapy was completed. No new development of blister or pustule. Palpebral conjunctival hyperaemia was absent. The body temperature was 37.4 degrees C. Covering was removed on the face. Additional drug application could be provided as needed when itching or pain with dryness occurred. Dimethylisopropylazulene was applied to erosion on the left upper extremity, followed by protection with gauze, etc. Erosion showed a tendency toward epithelization after the start of IVIg therapy, without new development of blister or other symptoms.
				16 days after discontinuation	The dose of prednisolone was reduced to 25 mg/day. Cutaneous symptoms showed a tendency to improve. Dimethylisopropylazulene was applied to erosion on the left upper extremity, followed by protection with gauze, etc.
				19 days after discontinuation	There was epithelization of erosion on the face, the right upper extremity, and the body trunk. Erosion on the area from the left shoulder to the upper arm persisted, but showed a tendency toward epithelization. Fading of erythema on the whole body had progressed.
				20 days after discontinuation	The patient was discharged. The dose of prednisolone was reduced to 20 mg/day.

29 days after discontinuation      A tendency toward epithelization became prominent, and the dose of prednisolone was reduced to 10 mg/day.

31 days after discontinuation      SJS showed a tendency toward regression, and then it was alleviated.

<Laboratory test values>

Test items (unit)	2 days before administration	Day 32 of administration	1 day after discontinuation	5 days after discontinuation	8 days after discontinuation	15 days after discontinuation
Bilirubin total (mg/dL)	0.7	0.5	0.6	0.6	0.7	-
γ-GTP (IU/L)	-	-	85	87	106	171
AST (GOT) (IU/L)	21	18	149	89	48	48
ALT (GPT) (IU/L)	19	17	238	152	98	58
White blood cell count (/mm <sup>3</sup> )	15 900	6 400	4 900	5 400	8 300	7 800
Eosinophils (%)	-	-	0	0	2	-
Lymphocytes (%)	-	-	4	13	13	-
Atypical lymphocytes (%)	-	-	0	0	0	-

<Results of skin biopsy>

1 day after the administration discontinuation      4-mm punch skin biopsy was performed from the site of erythema on the right abdominal region.  
 Pathological diagnosis: Superficial perivascular dermatitis with epidermal change, compatible with toxic eruption (Erythema on the right abdominal region)  
 Pathological findings: Epidermis showed an atrophy-like condition with solitary necrotizing cell clusters in some parts. Liquefaction degeneration was noted. A small amount of lymphocyte disseminated in the superficial dermal layer with extravascular erythrocytes in some parts. These findings are consistent with those of toxicoderma.

<Results of drug-induced lymphocyte stimulation test (DLST)>

2 days after the administration discontinuation      Additive-free culture, 433 cpm; Culture after PHA stimulation, 67287 cpm; SI (PHA), 155.4  
 This drug: Negative. Maximum S.I. was 0.8% and maximum response level was 351 cpm.  
 Lansoprazole: Negative. Maximum S.I. was 0.9% and maximum response level was 380 cpm.

<Results of ophthalmological examination>

2 days after the administration discontinuation      [Lens values]  
 R (Right eye):S:4.50, C:0.00, A:0, L (Left eye):S:4.50, C:0.00, A:0  
 [Intraocular pressure (mmHg)]  
 R (Right eye):AVG:12.0, L (Left eye):AVG:10.0  
 RV=0.5(0.8p×S+2.25D:C-1.25D Ax30), LV=0.2(0.7p×S+1.75D:C-1.00D Ax120)

[Reflex values]		[Kerato values]	
<R (Right)>		<Representative values>	
<L (Left)>		<R (Right)>	<L (Left)>
SPH-CYL, Axis,	SPH-CYL, Axis,	mm, D, deg:	mm, D, deg:
Reliability degree:	Reliability degree:	7.14, 47.25,168	7.24, 46.50, 164
2.25-1.25, 89, 8	1.75-1.00, 117, 7	7.03, 48.00,78	7.10, 47.50, 74
2.25-1.25, 90, 8	2.00-1.25, 116, 8	AVG:7.09,47.50	AVG:7.17,47.00
2.25-1.25, 91, 8	2.00-1.25, 118, 8	CYL:-0.75,168	CYL:-1.00,164
<2.25-1.25, 90>	<2.00-1.25, 117>		

[PD values]  
 Distance portion PD:59.0, Near portion PD:55.0

Concomitant drugs: betahistine mesilate, lansoprazole, bezafibrate, menatetrenone

# 4

## Revision of Precautions (No.307)

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 24, 2019.

### 1 Miscellaneous metabolism agents-miscellaneous

#### Baricitinib

**Branded name** Olumiant Tablets 2 mg, 4 mg (Eli Lilly Japan K.K.)

[Under New instructions]

**8. IMPORTANT PRECAUTIONS** (deleted)

**11. ADVERSE REACTIONS** Venous thromboembolism

**11.1 Clinically Significant Adverse Reactions** Pulmonary embolism and deep vein thrombosis may occur.  
(newly added)

### 2 Antineoplastics-miscellaneous

#### Osimertinib mesilate

**Branded name** Tagrisso Tablets 40 mg, 80 mg (AstraZeneca K.K.)

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions)** Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome, and erythema multiforme may occur. Patients should be carefully monitored and appropriate measures should be taken such as discontinuing this drug if any abnormalities are observed.  
(newly added)

[Under New instructions]

**11. ADVERSE REACTIONS** Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme  
**11.1 Clinically Significant Adverse Reactions**  
(newly added)

### 3 Synthetic antibiotics

#### Ofloxacin (oral dosage form)

**Branded name** Tarivid Tablets 100 mg (Alfresa Pharma Corporation), and the others

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions)** Tendon disorders such as Achilles tendonitis and tendon rupture: Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken. These tendon disorders are more likely to occur in patients with a history of organ transplant.  
(newly added)

**Peripheral neuropathy:** Peripheral neuropathy may occur. If symptoms such as numbness, muscle weakness, and pain are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4 Synthetic antibiotics

### **Garenoxacin mesilate hydrate**

**Branded name** Geninax Tablets 200 mg (Fujifilm Toyama Chemical Co., Ltd.)

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)**

**Peripheral neuropathy:** Peripheral neuropathy may occur. If symptoms such as numbness, muscle weakness, and pain are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

5 Synthetic antibiotics

### **Sitafloxacin hydrate**

**Branded name** Gracevit Tablets 50 mg, Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6 Synthetic antibiotics

### **[1] Ciprofloxacin**

### **[2] Ciprofloxacin hydrochloride hydrate**

**Branded name** [1] Ciproxan-I.V. 200 mg, 400 mg (Bayer Yakuhin, Ltd.), and the others  
[2] Ciproxan Tablets 100 mg, 200 mg (Bayer Yakuhin, Ltd.), and the others

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken. Cases of these symptoms that developed several months after the termination of this drug have been reported overseas.

7 Synthetic antibiotics

### **Tosufloxacin tosilate hydrate (oral dosage form)**

**Branded name** Ozex TAB. 75, 150, Fine Granules 15% for pediatric, TAB. 60 mg for pediatric (Fujifilm Toyama Chemical Co., Ltd.), Tosuxacin Tablets 75 mg, 150 mg (Mylan EPD G.K.), and the others

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions)**

**Peripheral neuropathy:** Peripheral neuropathy may occur. If symptoms such as numbness, muscle weakness, or pain are observed,



(newly added)

administration of this drug should be discontinued and appropriate measures should be taken.

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**Psychiatric symptoms:** Psychiatric symptoms such as hallucination and delirium may occur. Patients should be carefully monitored and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

8 Synthetic antibiotics

### Norfloxacin (oral dosage form)

**Branded name**

Baccidal Tablets 100 mg, 200 mg, Tablets for Children 50 mg (Kyorin Pharmaceutical Co.,Ltd.), and the others

[Under Old instructions]

**Adverse Reactions  
(Clinically Significant  
Adverse Reactions)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

9 Synthetic antibiotics

### Pazufloxacin mesilate

**Branded name**

Pasil Intravenous Drip Infusion 300 mg, 500 mg, 1000 mg (Fujifilm Toyama Chemical Co., Ltd.), Pazucross Injection 300 mg, 500 mg, 1000 mg (Mitsubishi Tanabe Pharma Corporation)

[Under Old instructions]

**Adverse Reactions  
(Clinically Significant  
Adverse Reactions)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

10 Synthetic antibiotics

### Pipemidic acid hydrate

**Branded name**

Dolcol Tablets 250 mg (Nichi-Iko Pharmaceutical Co., Ltd.), and the others

[Under Old instructions]

**Adverse Reactions  
(Clinically Significant  
Adverse Reactions)  
(newly added)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**Psychiatric symptoms:** Psychiatric symptoms such as depression and hallucination 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.

11 Synthetic antibiotics

### Prulifloxacin

**Branded name**

Sword Tablets 100 (Meiji Seika Pharma Co., Ltd.)

[Under Old instructions]

**Adverse Reactions  
(Clinically Significant  
Adverse Reactions)**

**Tendon disorders such as Achilles tendonitis and tendon rupture** may occur. If symptoms such as pain, edema, and redness around

(newly added)

the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken. Psychiatric symptoms such as delirium and memory disorder 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.

12 Synthetic antibiotics

### **Moxifloxacin hydrochloride (oral dosage form)**

**Branded name** Avelox Tablets (Bayer Yakuhin, Ltd.)

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken. Cases of these symptoms that developed several months after the termination of this drug have been reported overseas.

13 Synthetic antibiotics

### **Levofloxacin hydrate (oral, injectable dosage forms)**

**Branded name** Cravit Tablets 250 mg, 500 mg, Fine Granules 10%, Intravenous Drip Infusion Bag 500mg/100mL, 500mg/20mL (Daiichi Sankyo Co., Ltd.), and the others

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken. These tendon disorders are more likely to occur in patients with a history of organ transplant.

**Peripheral neuropathy:** Peripheral neuropathy may occur. If symptoms such as numbness, muscle weakness, or pain are observed, administration of this drug should be discontinued and appropriate measures should be taken.

14 Synthetic antibiotics

### **Lomefloxacin hydrochloride (oral dosage form)**

**Branded name** Bareon Capsule 100 mg, 200 mg (Mylan EPD G.K.)

[Under Old instructions]

**Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)**

**Tendon disorders such as Achilles tendonitis and tendon rupture:** Tendon disorders such as Achilles tendonitis and tendon rupture may occur. If symptoms such as pain, edema, and redness around the tendon are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**Psychiatric symptoms:** Psychiatric symptoms such as hallucination and delirium 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.

15 Biological preparations-miscellaneous

### **Tocilizumab (genetical recombination)**

**Branded name** [1] Actemra for Intravenous Infusion 80 mg, 200 mg, 400 mg (Chugai Pharmaceutical Co., Ltd.)

[2] Actemra Syringe for Subcutaneous Injection 162 mg, Auto-Injector for Subcutaneous Injection 162 mg (Chugai Pharmaceutical Co., Ltd.)

[Under Old instructions]  
**Adverse Reactions  
(Clinically Significant  
Adverse Reactions)  
(newly added)**

**Hepatic impairment:** Hepatic impairment associated with increased levels of AST, ALT and bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

[Under New instructions]  
**9. PRECAUTIONS  
CONCERNING PA-  
TIENTS WITH SPE-  
CIFIC BACKGROUNDS  
9.3 Patients with He-  
patic Impairment**

Precautions concerning patients with specific backgrounds

Patients with hepatic impairment  
Patients should be carefully monitored for an elevation in transaminase levels, etc.

**11. ADVERSE REAC-  
TIONS  
11.1 Clinically Signifi-  
cant Adverse Reac-  
tions  
(newly added)**

Hepatic impairment

Hepatic impairment associated with increased levels of AST, ALT and bilirubin, etc. may occur.

## 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 ADR 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 31 August, 2019)

⊙: Products for which EPPV was initiated after August 1, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
⊙	pH4-treated normal human immunoglobulin Privigen 10% I.V. Drip Infusion 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	CSL Behring K.K.	August 19, 2019
	Freeze-dried inactivated tissue culture rabies vaccine Rabipur for intramuscular injection	Glaxo Smith Kline K.K.	July 26, 2019
	Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate Symtuza Combination Tablets	Janssen Pharmaceutical K.K.	July 26, 2019
	Peficitinib hydrobromide Smyraf Tablets 50 mg, 100 mg	Astellas Pharma Inc.	July 10, 2019
	Ceftolozane sulfate/tazobactam sodium Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	June 25, 2019
	Guanfacine hydrochloride* <sup>1</sup> Intuitive Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	June 18, 2019
	Romiplostim (genetical recombination) * <sup>2</sup> Romiplate for s.c. injection 250 µg	Kyowa Hakko Kirin Co., Inc	June 18, 2019
	Tocilizumab (genetical recombination) * <sup>3</sup> Actemra Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	June 12, 2019
	Sodium selenite Aselend Injection 100 µg	Fujimoto Pharmaceutical Corporation	June 6, 2019
	Apalutamide Erleada Tablets 60 mg	Janssen Pharmaceutical K.K.	May 30, 2019
	Thiotepa Rethio Intravenous Infusion 100 mg	Sumitomo Dainippon Pharma Co., Ltd.	May 28, 2019
	Risankizumab (genetical recombination) Skyrizi Subcutaneous Injection 75 mg Syringe 0.83 mL	AbbVie GK	May 24, 2019
	Fluticasone furoate/vilanterol trifenate/umeclidinium bromide Trelegy 100 Ellipta 14 doses, 30 doses	Glaxo Smith Kline K.K.	May 22, 2019

Nonproprietary name		Name of the MAH	Date of EPPV initiate
Branded name on			
Esaxerenone	Minnebro Tablets 1.25 mg, 2.5 mg, 5 mg	Daiichi Sankyo Co., Ltd.	May 13, 2019
Mirogabalin besilate	Tarlige Tablets 2.5 mg, 5 mg, 10 mg, 15 mg	Daiichi Sankyo Co., Ltd.	April 15, 2019
Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate	Biktarvy Combination Tablets	Gilead Sciences Inc.	April 8, 2019
pH4- treated acidic normal human immunoglobulin (subcutaneous injection) *4	Hizentra 20% S.C. Injection 1g/5mL, 2g/10mL, 4g/20mL	CSL Behring K.K.	March 26, 2019
Tafamidis meglumine*5	Vyndaqel capsules 20 mg	Pfizer Japan Inc.	March 26, 2019
Landiolol hydrochloride*6	Onoact for Intravenous Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	March 26, 2019
Dupilumab (genetical recombination) *7	Dupixent Subcutaneous Injection 300 mg Syringe	Sanofi K.K.	March 26, 2019
Dapagliflozin propylene glycolate hydrate*8	Forxiga Tablets 5 mg, 10 mg	AstraZeneca K.K.	March 26, 2019
Nalmefene hydrochloride hydrate	Selincro tablets 10 mg	Otsuka Pharmaceutical Co., Ltd	Match 5, 2019
Romosozumab (genetical recombination)	Evenity subcutaneous injection 105 mg syringe	Amgen Astellas Bi-Pharma K.K.	March 4, 2019
Dacomitinib Hydrate	Vizimpro Tablets 15 mg, 45 mg	Pfizer Japan Inc.	March 1, 2019
Relugolix	Relumina Tablets 40 mg	Takeda Pharmaceutical Company Limited.	March 1, 2019
Lorazepam	Lora-pita Intravenous Injection 2mg	Pfizer Japan Inc.	March 1, 2019
Binimetinib	Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
Encorafenib	Braftovi Capsules 50 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
Sofosbuvir/velpatasvir	Epclusa Combination Tablets	Gilead Sciences Inc.	February 26, 2019
Metirosine	Demser Capsules 250 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
Taurine *9	Taurine powder 98% "Taisho"	Taisho Pharmaceutical Co., Ltd.	February 21, 2019
Damoctocog alfa pegol (genetical recombination)	Jivi for i.v. injection 250, 500, 1000, 2000, 3000 Refixia I.V. Injection 500, 1000, 2000	Bayer Yakuhin Ltd	February 12, 2019

\*1 Attention deficit/hyperactivity disorder (AD/HD) in adult patients

\*2 Aplastic anemia inadequately controlled with existing therapies

\*3 Cytokine release syndrome induced by tumor-specific T cell infusion treatment

\*4 Inhibiting progression of motor disability due to chronic inflammatory demyelinating polyneuropathy (in the cases where patients show an improvement in muscle weakness)

\*5 Transthyretin cardiac amyloidosis (wild type and mutant type)

- \*6 The following life-threatening arrhythmias when they are refractory and time-critical  
Ventricular fibrillation, ventricular tachycardia accompanied by haemodynamic instability
- \*7 Bronchial asthma (only for severe or refractory cases whose symptoms are not adequately controlled with existing treatments)
- \*8 Type 1 diabetes mellitus