Pharmaceuticals and Medical Devices Safety Information

No. 337 October 2016

Table of Contents

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

Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 337 October 2016

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

[Outline of Information]

P: Revision of Precautions *C*: Case Reports

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

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

Abbreviations

ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
Ca	Calcium
CC-A	Composite Component A
Cl	Chloride
CML	Chronic myeloid leukaemia
CND	Compliance and Narcotics Division
CP	Chronic phase
CPK	Creatinine phosphokinase
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
DLST	Drug lymphocyte stimulation test
DNA	Deoxyribonucleic acid
EAD	Economic Affairs Division
EPPV	Early post-marketing phase vigilance
FY	Fiscal year
GCN	Granule cell neuronopathy
GGTP	Gamma-glutamyl transpeptidase
GS 1	Global Standard One
HBc-Ab	Hepatitis B core antibody
HBs-Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HPB	Health Policy Bureau
HPV	Human papilloma virus
HSD	Health Service Division
JCV	JC virus
JIS	Japanese Industrial Standards
K	Potassium
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Na	Sodium
PCR	Polymerase chain reaction
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PTP	Press through package
RBC	Red blood cell count
SD	Safety Division
T-Bil	Total bilirubin
TEN	Toxic epidermal necrolysis
WBC	White blood cell count

1

Summary of the Relief System for Adverse Drug Reaction and Request of Cooperation for the System

1. Introduction

The Relief System for Adverse Drug Reaction (ADR) (hereinafter referred to as "the Relief System") was established in 1980 to bring prompt relief to people who suffer from adverse health effects such as disorders or disabilities caused by adverse reaction to pharmaceuticals or regenerative medical products (hereinafter referred to as "drugs") despite using such products properly. This is a public service funded by contributions from marketing authorization holders (MAHs) of pharmaceuticals as a way to fulfill part 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 using biological products despite proper use. Furthermore, adverse reaction to regenerative medical products and infections, etc. acquired through use of such products is now being covered by the Relief System since November 25, 2014.

The number of applications for the Relief System and payments of relief benefits has been increasing in recent years, and, since the establishment of the Relief System in 1980 until fiscal year (FY) 2015, over 18 000 cases have been granted relief benefits. However, awareness of the Relief System among the general public in FY2015 Note 1) was 29.6% in total: 8.0% who answered that they "were aware" of the Relief System and 21.6% who 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 ADR they have suffered because they are unaware of the Relief System.

Note 1) From "2015 Awareness Survey on the Relief System for ADR"
(only available in Japanese language)
https://www.pmda.go.jp/relief-services/adr-sufferers/0023.html

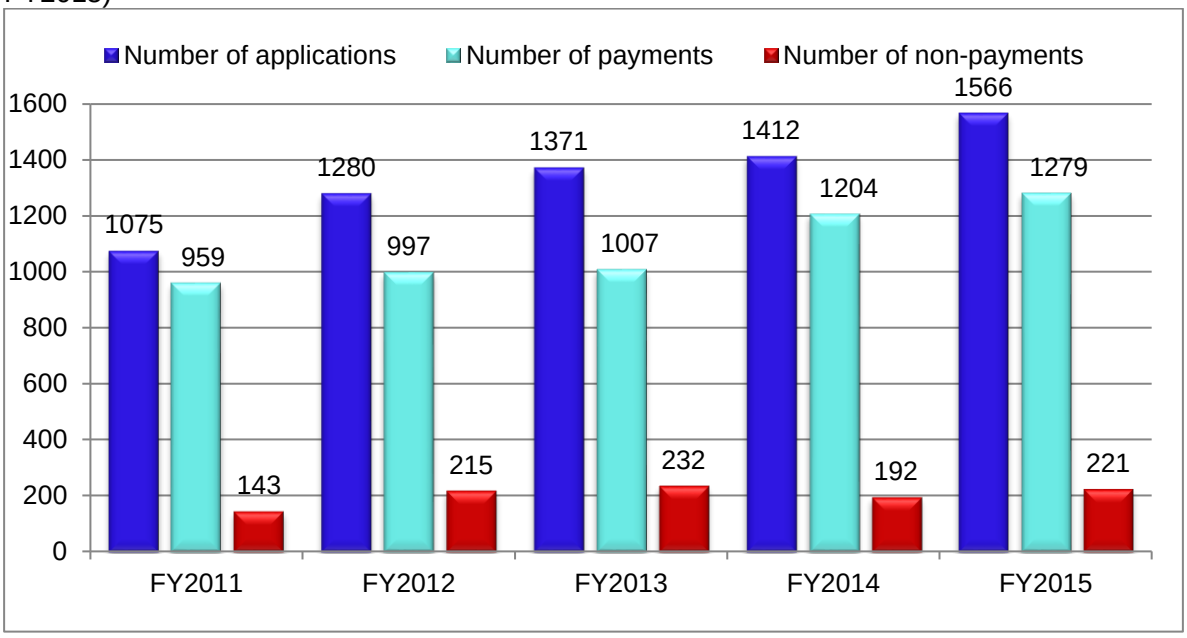
2. Status of payment/non-payment cases in the Relief System

Of the 6 469 cases assessed for the Relief System between FY2011 to FY2015, 5 466 (84%) were determined to be payment cases and 1 003 (16%) were determined to be non-payment cases (**Figure 1**). Details of reasons for non-payments are shown in **Figure 2**.

In addition, the goal of standard administrative processing time Note 2) from when Pharmaceuticals and Medical Devices Agency (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 FY2015 was 60.6%.

Note 2) The periods during which administrative processing cannot be conducted, because of the need for additional or supplemental documents from claimants and medical institutions for the purposes of making medical and pharmaceutical judgments, are excluded from the administrative processing time from claim submission to payment approval/rejection judgments.

Figure 1. Number of payments and non-payments under the Relief System for ADR (FY2011 to FY2015)

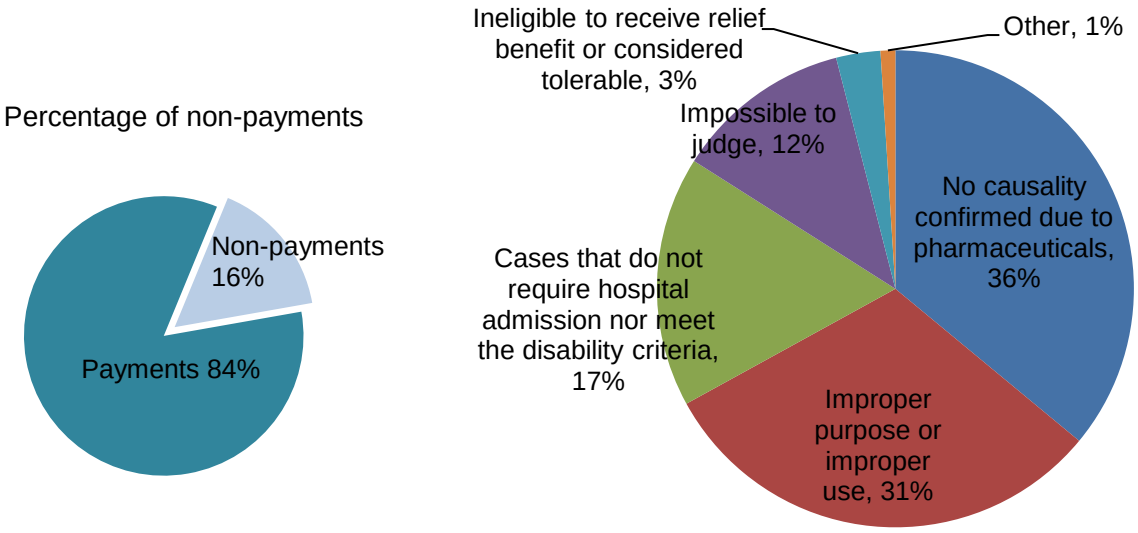


(Explanation for the figure)

*The number of cases is based on the number of applicants. Therefore, if there is a claim submitted for the same cause after the first claim was submitted, it is counted as 1 case.

*The number of applications and total number of payments and non-payments made within the FY are not consistent since a certain period is required from the receipt of the application to the decision on benefit payments.

Figure 2. Reasons for non-payments between FY2011 and FY2015



3. Adverse health effects subject to the Relief System

Adverse health effects subject to the Relief System include disorders (severe enough to require hospital admission), disabilities (serious enough to significantly limit daily life activities), and deaths despite proper use of drugs.

Drugs subject to 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 subjected 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 PMDA website (https://www.pmda.go.jp/english/relief-services/0002.html).

[Cases for which relief benefit payments were approved]
<Case 1> Case provided relief benefits for drug-induced liver injury due to use of preparations manufactured by pharmacies, etc.

After shofusan (K108) and inchinkoto preparations manufactured by pharmacies was taken by a female patient in her 10s, the patient developed drug-induced liver injury and was admitted to the hospital for treatment. Medical Expenses and Medical Allowance were paid.

<Case 2> Case provided Bereaved Family Pension and Funeral Expenses for anaphylactic (anaphylactoid) shock due to administration of antibiotics

After injectable sulbactam sodium/cefoperazone sodium (Cefon for intravenous injection) was administered to a male patient in his 80s, the patient suffered from an anaphylactic (anaphylactoid) shock and died from cardiac arrest. Medical Expenses, Medical Allowance, Bereaved Family Pension, and Funeral Expenses were paid.

<Case 3> Case provided Lump-sum Benefit for Bereaved Family and Funeral Expenses for thromboembolism due to administration of treatment for dysmennorrhoea

After drospirenone/ethinylestradiol (Yaz Combination Tablet) was taken by a female patient in her 10s, the patient developed a thromboembolism and died. Lump-sum Benefit for Bereaved Family and Funeral Expenses were paid.

<Case 4> Case provided Disability Pension for toxic epidermal necrolysis (TEN) (Lyell syndrome) due to administration of an over-the-counter drug

After Saridon A was taken by a female patient in her 20s, the patient developed TEN (Lyell syndrome) for which Medical Expenses and Medical Allowance was paid for. 9 years later, the patient developed visual impairment for which Disability Pension was paid.

4. Cases where proper use of pharmaceuticals could not be confirmed

Of the 1 003 non-payment cases between FY2011 to FY2015 Note 3), the reason for non-payment in approximately 30% was that proper purpose or method of use of the pharmaceutical could not be confirmed (**Figure 2**). The reason why the method of use was not considered proper most recently (in the last year or so) is presented in this section together with the description provided in package inserts or specific cases. **Table 1** shows the most common pharmaceuticals for which method of use was not considered proper.

Note 3) The number of cases is based on the number of applicants. Therefore, if there is a claim submitted for the same cause after the first claim was submitted, it is counted as 1 case.

Table 1. Number of cases for which method of use of the pharmaceutical was not considered proper (FY2011 to FY2015)

Name of causative drug	FY2011	FY2012	FY2013	FY2014	FY2015	Total (cases)
Lamotrigine	3	43	26	24	23	119
Thiamazole	6	7	1	2	5	21
Benzbromarone	3	3	1	1	1	9
Lithium carbonate	2	2	3	0	1	8
Salazosulfapyridine	2	1	1	1	2	7
Other	22	32	41	27	22	144
Total (cases)	38	88	73	55	54	308

(1) Cases where pharmaceuticals were used in ways other than the approved dosage and administration

The most common reason why the use of a pharmaceutical is not considered proper is that "use did not adhere to the approved dosage and administration", and cases using lamotrigine (Lamictal Tablets) account for a large majority of such uses. (Accounts for approximately 10% of the non-payment cases in FY2015).

Healthcare professionals should confirm the package insert once again and pay attention to the dosage and administration when using pharmaceuticals.

Improper use of lamotrigine

Incidence of skin disorders increases when lamotrigine is administered at doses or frequencies higher than recommended. Healthcare professionals have been repeatedly encouraged to adhere to the recommended administration and dosage, including dosage when initiating administration and dosage when titrating as well as alternate-day administration and when to titrate, through various means including the distribution of the Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) in February 2015.

At the same time, there are still many reports of non-payment cases because proper use was not confirmed.

Many of the cases where payment was not approved due to improper use included prescription of excessive dosages during initial administration or non-adherence to dose increase intervals.

Dosage and administration of lamotrigine is closely regulated in terms of dosages and dose increase intervals depending on specific indications and concomitant pharmaceuticals.

Healthcare professionals should comply with the dosage and administration.

The incidence of skin disorders increases when this drug is administered more frequently or at a higher dose than approved.

- During the initial administration, this drug should not be used more frequently or at higher doses than the approved dosage and administration.
- When used concomitantly with sodium valproate, his drug should only be administered on alternate-days for the first two weeks (only for adult patients).
- This drug should not be used more frequently or at higher doses than the approved dosage and administration during dose titration until maintenance dosage is achieved.
- A dose increase should not be attempted earlier than the specified timing.

Healthcare professionals should make an effort towards early detection and treatment of skin disorders.

- The following symptoms in addition to rash may indicate the development of serious skin disorders. Administration of this drug should be discontinued immediately should such symptoms be observed.
  - ○ Pyrexia (38°C and above)
  - ○ Ocular hyperaemia
  - ○ Lip/oral mucosa erosion
  - ○ Pharyngodynia
  - ○ General malaise
  - ○ Lymphadenopathy, etc.
- Delay in treatment of skin disorders might lead to a serious outcome. Healthcare professionals should consult with a dermatologist at an early stage, and appropriate measures should be taken.
- Patients or family members should be advised to seek medical attention immediately and should inform the doctor/pharmacist that they are being treated with this drug if a rash and/or the above symptoms occur.

From the Dear Healthcare Professionals Letter of Rapid Communication in February 2015 "Serious skin disorders caused by Lamictal Tablets"

Case 1 Case with maculopapular drug eruption due to lamotrigine, etc.

The drug was used in a female patient in her 20s to prevent relapse/recurrence of mood episodes for bipolar disorder. It was prescribed without any concomitant use of sodium valproate and pharmaceuticals to induce glucuronidation. Lamotrigine was initiated at 25 mg/day and dose was increased to 50 mg/day from Day 9, which is not considered proper use.

When using lamotrigine to suppress relapse/flare-up of mood episodes for bipolar disorder (without concomitant use of sodium valproate and without concomitant use of pharmaceuticals to induce glucuronidation of lamotrigine), the Dosage and Administration section of the package insert

for lamotrigine indicates that “as a general rule, lamotrigine should be orally administered once daily at a dose of 25 mg/day for the first two weeks. For the following two weeks, lamotrigine should be orally administered once daily at a dose of 50 mg/day. From Week 5, lamotrigine can be orally administered either once daily or twice daily at a dose of 100 mg/day.” Dose increase at a time earlier than specified is not considered proper use.

Mon	Tue	Wed	Thu	Fri	Sat	Sun
1	2	3	4	5	6	7
25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg
8	9	10	11	12	13	14
25 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg
15	16	17	18	19	20	21
50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
22	23	24	25	26	27	28
100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

⇐ Improper
⇐ Proper

<Thoughts for alternate-day administration>

◌ If lamotrigine is used concomitantly with sodium valproate in bipolar disorder

The Dosage and Administration section of the package insert for lamotrigine indicates “as a general rule, lamotrigine is administered on alternate-days for the first two weeks at a dose of 25 mg/day, and orally administered once daily at a dose of 25 mg/day for the following two weeks.” Proper use will not be accepted unless Day 14 is a rest period and consecutive administration begins from Day 15.

Mon	Tue	Wed	Thu	Fri	Sat	Sun
1	2	3	4	5	6	7
○	×	○	×	○	×	○
8	9	10	11	12	13	14
×	○	×	○	×	○	○
						×
15	16	17	18	19	20	21
○	○	○	○	○	○	○
22	23	24	25	26	27	28
○	○	○	○	○	○	○

⇐ Improper
⇐ Proper

Healthcare professionals are encouraged to cooperate with proper use.

(2) Case in which required tests were not conducted

If package inserts specify that certain tests must be conducted for use of pharmaceuticals and these tests are not conducted, method of use will not be considered proper.

Tests not conducted when using thiamazole

71% of the reported agranulocytosis due to use of thiamazole was reported within 2 months after initiating administration, and the Warning section of the package insert specifies that “as a general rule, blood tests including differential white blood cell count (WBC) must be conducted once every 2 weeks at least for the first two months and periodically after that.” Healthcare professionals have been encouraged to exercise caution including notifications from pharmaceutical companies on proper use, etc., and other various means using a variety of materials; however, there have been reports of cases where tests are not performed.

Case 2 Cases of agranulocytosis with use of thiamazole

No blood tests were performed for a female patient in her 30s after administration of thiamazole (Mercazole Tablets) for 2 months. While low WBC was confirmed in the blood test performed after 2 months, administration of thiamazole was continued for another two weeks; therefore, method of use was not considered proper.

Description noted on package insert
[Warning]
1. Serious agranulocytosis mainly occurs within 2 months after initiating administration, and there have been fatal cases reported as well. As a general rule, blood tests including differential WBC must be performed once every 2 weeks at least for the first two months and periodically after that. If abnormalities such as decrease in granulocytes are observed, administration of the drug should be discontinued immediately and appropriate measures should be adopted. In addition, when re-initiating administration after discontinuation, similar caution should be exercised. (Refer to the "Clinically significant adverse reaction" section)
2. Before administering this drug, the patient should be informed that agranulocytosis, etc. may occur as ADR and tests must be conducted, and the patient should be instructed as follows.
(1) Immediately contact your primary physician when symptoms of agranulocytosis (pharyngeal pain, pyrexia, etc.) occur.
(2) As a general rule, periodic blood tests must be performed once every 2 weeks at least for the first two months after initiating administration; therefore, please come to the hospital accordingly.
[Clinically significant adverse reaction]
1) Pancytopenia, aplastic anaemia, agranulocytosis, leukopenia (unknown frequency):
Pancytopenia, aplastic anaemia, agranulocytosis, or leukopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued immediately, and appropriate measures should be adopted. (Refer to the "Warnings" section)

In order to detect ADR early and prevent it from becoming serious, healthcare professionals are encouraged to use the drug properly according to the "Precautions for use" as tests for early detection of ADR and explanation to patients regarding the need for such tests are considered important.

Alert for Proper Use of Drugs
https://www.pmda.go.jp/english/safety/info-services/drugs/properly-use-alert/0001.html

5. Source of information on the Relief System for Adverse Drug Reaction

Details of this Relief System as well as the Infections derived from Biological Products Relief System can be found on PMDA's website (http://www.pmda.go.jp/relief-services/adr-sufferers/0001.html [only available in Japanese language]). Furthermore, materials on the Relief System for patients is also available on the website, and healthcare professionals are encouraged to use these materials to disseminate information on the Relief System.

Necessary documents for making claims can be downloaded from the following website and can be created using a computer, etc.
Furthermore, if the documents are created using a computer, etc., claimants are requested to submit the paper-based documents as well as provide an electronic copy of the electronic file using a CD, etc.
http://www.pmda.go.jp/relief-services/adr-sufferers/0004.html [only available in Japanese language]
Details of medical certificates and certificates for prescription/use are important information when judging whether or not use was proper, etc.; therefore, as much detail as possible should be included in these documents.

Please note that the following cases will not be applicable to receive 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 where it is clear who is responsible for payment of damages such as MAHs. Note 4)
C. Cases where it is necessary to use the pharmaceutical in an amount exceeding the approved dosage for the purpose of saving the patient's life, even if it was recognized beforehand that adverse health effects may occur. Note 5)

D. Cases where purpose/method of use is not confirmed to be proper (such as cases where pharmaceuticals are used in ways other than indications approved by the Minister of Health, Labour and Welfare, or cases where pharmaceuticals have not been used in accordance with the Precautions section of package inserts).
E. Cases of adverse health effects resulting from drugs not considered eligible for the Relief System. Pharmaceuticals not considered eligible include:
   i. Pharmaceuticals used in 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 ADR, 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 (including a hospital administration in which treatment equivalent to inpatient care is not required) or cases where disabilities caused by pharmaceuticals fail to meet the disability criteria under the Relief System. Note 6)
   Or cases that fail to meet the following criteria: "Disability that results in significant limitation during his/her daily life performance (Grade 2)"
G. Cases where 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 of Ministry of Health, Labour and Welfare (MHLW) based on medical and pharmaceutical judgment.
   - Cases where the disorders or disabilities are considered to be unlikely to be caused by ADR (those that are not considered to be due to drugs)
   - Cases where it cannot be judged whether there are causalities or whether pharmaceuticals are used for the proper use and with the proper method, because of insufficient documentation (impossible to judge)

Note 4) "Person responsible for payment of damages" typically refers to person in charge, etc. for accidents due to adulterated drugs such as mutated drugs or contaminated drugs"

Note 5) If the sufferer's acceptance towards 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 for critical care situations
(2) There are no alternative treatment modalities available
(3) A higher dose of the pharmaceutical than the recommended dose is used
(4) The possibility of adverse health effects due to ADR was recognized in advance
(5) Adverse health effects due to ADR which were recognized in advanced mentioned in (4) occurred
Whether individual cases will be accepted will be judged based on these typical situations. In order for the claim to be considered acceptable, a 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 the typical case from an overall standpoint including other situations or factors, etc.

Note 6) 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 limitation during his/her daily life performance (Grade 2)"

6. Closing comments

Healthcare professionals are encouraged to thoroughly read the package inserts before using pharmaceuticals and to use them properly. Please note that cases where pharmaceuticals 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 ADR related to drugs.

If ADR, etc. occurs or if healthcare professionals are consulted by their patients about ADR, healthcare professionals should provide information on the Relief System to the patient or family members if the adverse health effect is possibly applicable to receive relief benefits under the Relief System. MHLW/PMDA encourages continued cooperation from healthcare professionals in preparing documents, such as medical certificates, required to claim these relief benefits.

The following consultation service in regards 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)
  Email: kyufu@pmda.go.jp

Relief Efforts for Human Papilloma Virus Vaccine through the Relief System for Adverse Drug Reaction

1. Introduction

The joint meeting of the Adverse Reaction 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 regards to the human papilloma virus vaccine (cervical cancer prevention vaccines, hereinafter referred to as "HPV vaccines") was held on September 17, 2015. During this meeting, results from the national tracking survey was presented. According to the findings, after HPV vaccines were administered, a large number of people suffered from various symptoms not localized to the injection site such as pain and numbness, which affected the people's lives such as being unable to go to school or work.

Based on these results, the Relief System will provide relief benefits as much as possible to claimants who claim adverse health effects such as pain after administration of HPV vaccines, and MHLW/PMDA have taken efforts to increase awareness of the Relief System. MHLW will continue to offer necessary support for patients while promptly reviewing the relief claims.

2. Efforts regarding relief benefits after administration of HPV vaccines, etc.

1) Administrative notice issued on October 22, 2015 by the Health Service Division (HSD)/Safety Division (SD) "(Request for) Increasing awareness of deadlines for Relief System for ADR claims in relation to administration based on "Urgent Vaccination Promotion such as for cervical cancer vaccines"."
2) Administrative notice issued on December 1, 2015 by HSD "(Request for) Relief benefits for adverse health effects due to Urgent Vaccination Promotion such as for cervical cancer vaccines". *1
3) Administrative notice issued on January 14, 2016 by SD "Items to be considered in regards to necessary documentation when claiming relief benefits under the Relief System for ADR in relation to administration based on "Urgent Vaccination Promotion such as for cervical cancer vaccines"." *2
4) Notification issued on January 15, 2016 for each medical association, etc. "Request of cooperation for Relief System for Adverse Health Effects provided by PMDA" (Office of ADR, Pharmaceutical Safety and Environmental Health Bureau (PSEHB) Notification No. 0115-1, and PSEHB/SD Notification No. 0115-1).
5) Established Subcommittee on Evaluation of Adverse Reactions of HPV Vaccines on April 1, 2016 in order to streamline reviews related to adverse reactions of HPV vaccines.

3. Relief benefits for adverse health effects due to "Urgent Vaccine Promotion such as for cervical cancer vaccines" (Related to Notification*1)

Adverse health effects in people who were vaccinated with vaccines applicable to the relevant promotional business Note) are regarded to be ADR based on the review results of the relief benefits. For example, even if the medical care required was not enough to be considered inpatient care, such as if patients received treatment on an outpatient basis, the patient may be eligible to receive support for medical expense/medical allowance payments from Public Foundation of the Vaccination Research Center.

If support for medical expense/medical allowance is to be provided for the first time, claims for relief benefits must first be submitted for the Relief System; therefore, healthcare professionals are requested to cooperate with claimant's procedures (creating medical certificates, etc.).

Note) Females who are first year junior high students (approximately 13 years old) to those who are first year high school students (approximately 16 years old) in whom HPV vaccines were administered during November 26, 2010 to March 31, 2013 are possibly eligible to receive relief benefits.

http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/sesshu_youryou.pdf [only available in Japanese language]

4. Items to be considered in regards to necessary documentation when claiming relief benefits under the Relief System for Adverse Drug Reaction in relation to HPV vaccines, etc. (Related to Notification*2)

MHLW issued an administrative notice on January 14, 2016 regarding items to be considered in regards to necessary documentation when claiming relief benefits.

1. About medical certificates

(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 for medical certificates to be created by all medical institutions they visited.

(2) For the medical certificates, information necessary to judge the causal relationship with the vaccination such as information regarding day of vaccination and the clinical course until onset of symptoms are considered important and should be provided as much as possible. Furthermore, it is permissible for the medical institution creating the medical certificate to include information other than treatment (for example, information related to the duration of clinical practice where the patient consulted multiple medical institutions since the symptoms were not apparent, symptoms that triggered hospital consultation, etc.).
Please also cooperate in attaching as materials related to other medical institutions (addresses, telephone numbers, day 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 materials that only have partial information.

2. About 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 for vaccination coupons provided prior to vaccination or other reference materials (such as body temperature results, items asked during medical interview or examined) and attach these to the claims.

From the administrative notice issued on January 14, 2016 by SD "Items to be considered in regards to necessary documentation when claiming relief benefits under the Relief System for ADR in relation to administration based on "Urgent Vaccination Promotion such as for cervical cancer vaccines"."

(References)

Notification issued September 30, 2015 "Enhancing consultation/support services for those who developed symptoms after vaccination for HPV infections" (Health Safety Bureau, MHLW Notification No. 0930-7-27, Sports and Youth Bureau, Ministry of Education, Culture, Sports, Science and Technology Notification No. 419)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/madoguchi/dl/151116_02.pdf [only available in Japanese language]

Administrative notice issued on October 22, 2015 by HSD/SD "(Request for) Increasing awareness of deadlines for the Relief System for ADR claims in relation to administration 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 available in Japanese language]

Administrative notice issued on December 1, 2015 by HSD "(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 available in Japanese language]

Administrative notice issued on January 14, 2016 by SD "Items to be considered in regards to necessary documentation when claiming relief benefits under the Relief System for ADR in relation to administration based on "Urgent Vaccination Promotion such as for cervical cancer vaccines""
https://www.pmda.go.jp/files/000209731.pdf [only available in Japanese language]

Notification issued on January 15, 2016 for each medical association, etc. "Request of cooperation for the Relief System for Adverse Health Effects provided by PMDA" (Office of ADR, PSEHB

Notification No. 0115-1, and PSEHB/SD Notification No. 0115-1)
https://www.pmda.go.jp/files/000209915.pdf [only available in Japanese language]
About the 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 available in Japanese language]

2

Amendment of Procedures for Bar Code Labeling on Prescription Drugs

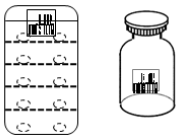
1. Introduction

On August 30, 2016, a notification was issued to seek to expand the scope of descriptions on the bar code labeling on distribution packaging units and supply packaging units of prescription drugs. This section will provide an overview of the notification.

2. Specific revisions to the procedures

Products subject to bar code labeling are prescription drugs ([1] specified biological products, [2] biological products, [3] injections, [4] oral agents, and [5] topical agents). Packaging form units are classified into the following 3 types: I) dispensing packaging unit, II) distribution packaging unit, and III) supply packaging unit. In the recently revised "Procedures for Bar Code Labeling on Prescription Drugs", bar code labeling (i.e. Global Standard One [GS 1] data bar specified by the Japanese Industrial Standards [JIS] X0509 or Code 128 specified by JIS X0504) of commodity code, expiration date, quantity, and lot number or code are required according to the type of prescription drugs and packaging form units as shown in the following **Table**.

<Prescription drugs subject to bar code labeling>

Type of prescription drug	I) Dispensing packaging unit  Press through package (PTP) sheets, vials, etc.			II) Distribution packaging unit  Boxes containing 10 PTP sheets, etc.			III) Supply packaging unit  Cartons containing 10 distribution packaging units, etc.			
	Commodity code	Expiration date	Lot number or code	Commodity code	Expiration date	Lot number or code	Commodity code	Expiration date	Lot number or code	Quantity
(1) Specified biological products	a	a	a	a	a	a	a	a	a	a
(2) Biological products	a	b	b	a	a	a	a	a	a	a
(3) Injections	a	b	b	a	a*	a*	a*	a*	a*	a*
(4) Oral agents	a	b	b	a	a*	a*	a*	a*	a*	a*
(5) Topical agents	a	b	b	a	a*	a*	a*	a*	a*	a*

Note 1: "a" indicates items that must be labeled (required labeling) and "b" indicates items that do not necessarily have to be labeled (optional labeling)

Note 2: Items marked with "*" are items that must be bar code labeled if shipped by MAHs in April 2021 onwards (April 2023 onwards for products with special reasons)

Recently, items previously under optional labeling for distribution packaging units and supply packaging units (i.e. items marked with "*" in Note 2 of the table [Expiration date and lot number or code, with quantity and commodity code for supply packaging units.]) will now be subjected to

required labeling in order to streamline distribution and strengthen traceability. (Please refer to [Reference Notifications])

As a general rule, new bar code labeling that includes variable information without any exceptions will be placed on products shipped from MAHs from April 2021 onwards. These labels will be used to manage distribution records, allowing more prompt and reliable confirmation and management of lot numbers, etc. at the distribution stage. This is considered an effective method to appropriately execute important responsibilities of MAHs, etc. in terms of safety measures including recall of products, suspension of sales and provision of essential information.

<Bar code labeling including expiration date, lot number or code in addition to the commodity code>

Distribution packaging unit (Dispensing packaging unit)

GS 1 data bar limited composite symbol Composite Component A (CC-A)

(Reference): GS 1 data bar limited

(Note) Only includes information on the commodity code

Supply packaging unit

GS1-128 (Code 128)

3. Utilization of bar code labeling

During the “(24th) Conference regarding improvement in distribution of prescription drugs” held on April 15, 2016, it was announced that rate of bar code labeling (for “commodity code”) was almost 100% for dispensing packaging units of oral and topical agents in addition to specified biological products, biological products, and injections that had been subjected to required labeling.

Hereafter, studies on actual utilization of bar code labeling of prescription drugs among medical institutions, pharmacies, etc. nationwide is scheduled for FY2016 Health and Labour Sciences Special Research Project “Study on actual utilization of bar code labeling of prescription drugs in order to promote utilization for safety measures and recommendations on modifications to labels, etc.”

Healthcare professionals are encouraged to proactively utilize bar code labeling for cross-checking as an effective measure to prevent medical accidents due to mix-up of prescription drugs.

[Reference Notifications]
Partial amendment of the “Procedure for Bar Code Labeling on Prescription Drugs”
(Joint Notification of Health Policy Bureau (HPB)/Economic Affairs Division (EAD) No. 0830-1, PSEHB/SD No. 0830-1, and PSEHB/Compliance and Narcotics Division (CND) No. 0830-1, by the Director of EAD, HPB, MHLW, by the Director of SD, PSEHB, and by the Director of CND, PSEHB dated August 30, 2016)

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated August 4 and September 13, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 (a) Imatinib mesilate, (b) Dasatinib hydrate

Brand name (name of company)	(a) Glivec Tablets 100 mg (Novartis Pharma K.K.), and others (b) Sprycel Tablets 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	(a) 1. Chronic myeloid leukaemia (CML) 2. KIT (CD117) - positive gastrointestinal stromal tumor 3. Philadelphia chromosome - positive acute lymphocytic leukaemia 4. The following FIP – 1 - like 1 – platelet - derived growth factor receptor alpha - positive diseases: Hypereosinophilic syndrome, chronic eosinophilic leukaemia (b) 1. CML 2. Recurrent or refractory Philadelphia chromosome – positive acute lymphocytic leukaemia

PRECAUTIONS (underlined parts are revised)

Important Precautions

<u>Reactivation of hepatitis B virus (HBV) may occur among hepatitis B virus carriers or patients who have a history of being infected (i.e. HBs-Ag negative and HBc-Ab or HBs-Ab positive) following administration of Bcr-Abl tyrosine kinase inhibitors. The presence or absence of HBV infection should be confirmed prior to administrating this drug and appropriate measures should be adopted before the administration of this drug. After beginning the administration of this drug, attention should be paid to the occurrence of signs or symptoms related to reactivation of the HBV through continuous hepatic function tests, monitoring of hepatitis virus markers, etc.</u>

Adverse reactions (clinically significant adverse reactions)

Infections: Infections such as pneumonia and sepsis may occur. <u>Reactivation of HBV may also occur.</u> Patients should be carefully monitored through periodical blood test, etc. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 2 months (April 2013 to June 2016).
Cases related to reactivation of the HBV:
(a) 1 case (no fatal case)
(b) 0 cases
The number of patients using the drug estimated by the MAH in the past 1 year:
(a) Approximately 8 000
(b) Approximately 4 500

Launched in Japan:
(a) December 2001
(b) March 2009

(c) Nilotinib hydrochloride hydrate

Brand name (name of company)	(c) Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	(c) CML in chronic phase (CP) or accelerated phase

PRECAUTIONS (underlined parts are revised)

Important Precautions

Reactivation of hepatitis B virus (HBV) may occur among hepatitis B virus carriers or patients who have a history of being infected (i.e. HBs -Ag negative and HBc-Ab or HBs Ab positive) following administration of Bcr-Abl tyrosine kinase inhibitors. The presence or absence of HBV infection should be confirmed prior to administrating this drug and appropriate measures should be adopted before the administration of this drug. After beginning the administration of this drug, attention should be paid to the occurrence of signs or symptoms related to reactivation of the HBV through continuous hepatic function tests, monitoring of hepatitis virus markers, etc.

Adverse reactions (clinically significant adverse reactions)

Infections: Infections such as pneumonia and sepsis may occur. Reactivation of HBV may also occur. Patients should be carefully monitored through periodical blood test, etc. If any abnormalities are observed, dose of this drug should be reduced or administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 2 months (April 2013 to June 2016).
Cases related to reactivation of the HBV:
(c) 0 cases
The number of patients using the drug estimated by the MAH in the past 1 year:
(c) Approximately 2 900
Launched in Japan:
(c) March 2009

(d) Bosutinib hydrate

Brand name (name of company)	(d) Bosulif Tablets 100 mg (Pfizer Japan Inc.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	(d) CML resistant or intolerant to prior drugs

PRECAUTIONS (underlined parts are revised)

Important Precautions

Reactivation of hepatitis B virus (HBV) may occur among hepatitis B virus carriers or patients who have a history of being infected (i.e. HBs -Ag negative and HBc-Ab or HBs Ab positive) following administration of Bcr-Abl tyrosine kinase inhibitors. The presence or absence of HBV infection should be confirmed prior to administrating this drug and appropriate measures should be adopted before the administration of this drug. After beginning the administration of this drug, attention should be paid to the occurrence of signs or symptoms related to

reactivation of the HBV through continuous hepatic function tests, monitoring of hepatitis virus markers, etc.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 2 months (April 2013 to June 2016).
Cases related to HBV:
(d) 0 cases
The number of patients using the drug estimated by the MAH in the past 1 year:
(d) Approximately 330
Launched in Japan:
(d) December 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Female 30s	CML (carrier of hepatitis virus, asymptomatic gene carrier, gastric ulcer, myalgia)	400 mg for 148 days 300 mg for 210 days	**Hepatitis B, drug interaction, liver disorder** [Patient background] Asymptomatic carrier of HBV 13 days before administration HBV-deoxyribonucleic acid (DNA) 3.9 log copies/mL 6 days before administration Diagnosed with CML-CP. Day 1 of administration Once daily administration with 400 mg imatinib mesilate was initiated. Day 94 of administration Negativation of HBV-DNA (undetected using polymerase chain reaction [PCR]) Day 148 of administration (Day of discontinuation) Increase in creatnine phosphokinase (CPK) was confirmed and administration of this drug was discontinued. 16 days after discontinuation (Day of re-administration) Once daily administration with 300 mg imatinib mesilate was re-initiated. Day 35 of re-administration HBV-DNA 2.9 log copies/mL Day 56 of re-administration HBV-DNA 3.4 log copies/mL Day 83 of re-administration HBV-DNA 3.9 log copies/mL Day 104 of re-administration HBV-DNA 4.1 log copies/mL, and the patient was diagnosed with reactivation of HBV. Day 118 of re-administration Consultation with department of hepatology of Hospital A. Day 125 of re-administration Initiate oral treatment with Entecavir 0.5 mg. Day 132 of re-administration Twice daily administration with 200 mg/day ursodeoxycholic acid was initiated. Day 210 of re-administration (Day of discontinuation of re-administration) The patient was confirmed to be suffering from liver

				disorder (aspartate aminotransferase [AST] 144, alanine aminotransferase [ALT] 167), and administration of imatinib mesilate was discontinued due to possible drug interaction. Three times daily administration with 1 tablet/day glycyrrhizinate was initiated. 49 days after discontinuation of re-administration Peak of liver disorder (AST 280, ALT 354) 77 days after discontinuation of re-administration Discontinue administration of ursodeoxycholic acid and glycyrrhizinate. 92 days after discontinuation of re-administration Treatment for CML-CP with 300 mg/day nilotinib initiated. 105 days after discontinuation of re-administration Normalization of hepatic function (AST 28, ALT 25) 112 days after discontinuation of re-administration HBV-DNA resolved to <2.1 log copies/mL. Hepatitis B outcomes recovered. Drug interaction and liver disorder outcomes recovered.

Laboratory examination

	13 days before administration	Day 94 of administration	Day 35 of re-administration	Day 56 of re-administration	Day 83 of re-administration
ALT (IU/l)	14		17		16
AST (IU/l)	19		25		24
ALP (IU/l)	156		256		197
T-Bil (mg/dl)	0.68		1.07		0.84
LDH (IU/l)	267		210		189
GGTP (IU/l)	20		17		15
HBV-DNA (PCR) (log copies/mL)	3.9	Undetected	2.9	3.4	3.9
HBs Ag	+				
HBs Ab	-				
HBe Ag	-				
HBe Ab	+				
HBc Ab	+				

	Day 104 of re-administration	Day 125 of re-administration	Day 210 of re-administration (Day of discontinuation of re-administration)	49 days after discontinuation of re-administration	112 days after discontinuation of re-administration
ALT (IU/l)	20	67	167	354	25
AST (IU/l)	25	59	144	280	29
ALP (IU/l)	207	207	210		238
T-Bil (mg/dl)	0.66	0.71	1.05	1.16	1.88
LDH (IU/l)	204	217	258	278	189
GGTP (IU/l)	16	18	26		25
HBV-DNA (PCR) (log copies/mL)	4.1	4.1	2.2	2.7	<2.1

Concomitant medications: Entecavir hydrate, rabeprazole sodium, eperisone hydrochloride

2 Afatinib maleate

Brand name (name of company)	Giotrif Tablets 20 mg, 30 mg, 40 mg, 50 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	*EGFR* mutation-positive unresectable or relapsed non–small-cell lung cancer

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

TEN, oculomucocutaneous syndrome (Stevens–Johnson syndrome), and erythema multiforme:
Serious bullous or exfoliative skin disorders such as TEN, oculomucocutaneous syndrome, and erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 3 months (April 2013 to July 2016).
Cases related to TEN: 2 case (no fatal case)
Cases related to erythema multiforme: 1 case (no fatal case)
The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 5 400 (July 2015 to June 2016)
Launched in Japan: May 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Lung neoplasm malignant (bone neoplasm, brain neoplasm, hypertension, EGFR gene mutation)	40 mg for 7 days ↓ 30 mg for 6 days	**TEN** 1 year and 8 months before administration Oral administration of gefinitib was initiated. Radiation therapy performed for bone metastasis (Th12). 9 months before administration Administration of carboplatin + pemetrexed sodium hydrate + bevacizumab was initiated. 6 months before administration Gamma knife therapy performed for brain metastasis. Administration of docetaxel hydrate was initiated. 1 month before administration The patient was admitted to the hospital due to increase or proliferation of brain metastasis. Whole-brain irradiation was initiated. Onset of cancerous meningitis. Worsening of physical status. Day 1 of administration Administration of this drug was initiated. Day 7 of administration (Day of discontinuation) Onset of diarrhoea (non-serious). Suspend administration of this drug. Administration of loperamide hydrochloride was initiated. 1 day after discontinuation Administration of butyric acid bacteria formulations (60 mg/day) was initiated. 5 days after discontinuation

Diarrhoea recovered.
6 days after discontinuation (Day of re-administration)
The dosage of this drug was decreased and administration was re-initiated.
Day 6 of re-administration (Day of discontinuation of re-administration)
Discontinue administration of this drug.
1 day after discontinuation of re-administration
Onset of strong generalized itching with blisters. Hospital admittance was prolonged due to this event.
Administration of olopatadine hydrochloride and betamethasone butyrate propionate was initiated.
2 days after discontinuation of re-administration
Torso, arms, and ears: Onset of moderate bullous eruption, moderate erosion, and moderate Nikolsky's sign.
Neck, torso, lower limbs, arms, legs, and ears: Onset of severe erythema multiforme.
5 days after discontinuation of re-administration
Exacerbation of eruption. Steroid pulse therapy (methylprednisolone sodium succinate, 1 000 mg/day × 3 days) was initiated.
6 days after discontinuation of re-administration
The results of skin biopsies from two locations were consistent with Stevens-Johnson syndrome, and the dermatologist diagnosed the patient with TEN. Silicon mesh sheet (Mepitel One) was initiated.
8 days after discontinuation of re-administration
Dosage of prednisolone was decreased to 60 mg/day.
13 days after discontinuation of re-administration
Dosage of prednisolone was decreased to 50 mg/day.
18 days after discontinuation of re-administration
Dosage of prednisolone was decreased to 40 mg/day.
20 days after discontinuation of re-administration
Dosage of prednisolone was decreased to 30 mg/day.
23 days after discontinuation of re-administration
TEN was resolving. Dosage of prednisolone was decreased to 20 mg/day. Dermatological procedures were completed due to epitheliazation and moisturizing was continued.

Laboratory examination

	1 day before administration	5 days after discontinuation	6 days after discontinuation	13 days after discontinuation	23 days after discontinuation
Temp (°C)	37.2	37.3	–	37.2	36.9
WBC (cells/μL)	8000	3400	–	4200	7600
CRP (mg/dL)	0.11	–	–	–	–
DLST	–	–	Negative	–	–

Concomitant medications: Butyric acid bacteria formulation, loperamide hydrochloride, dexamethasone

3 Corticorelin (human)

Brand name (name of company)	hCRH “TANABE” Injection 100 mg (Mitsubishi Tanabe Pharma Corporation)
Therapeutic category	Various functional testing reagents
Indications	Secretory function test of hypothalamic, pituitary, and adrenocortical hormone <Judgment criteria> Secretory function is determined by the blood adrenocorticotropic hormone (ACTH) level and the blood cortisol level. Because the blood ACTH level varies depending on measurement methods, the time-of-day of testing, and other conditions, normal response criteria should be developed in each institution. When the testing is performed for a healthy individual at around 9:00 a.m., radioimmunoassay measurement normally shows that the blood ACTH level (approximately 15 pg/mL before administration) reaches the maximum level 30 minutes after administration to approximately 3 times the level before administration. However, when the blood ACTH level 30 minutes after administration alone is considered insufficient as the basis to determine the secretory function, it is desirable that the blood ACTH level is chronologically measured after administration to determine the secretory function. Because the blood cortisol level varies depending on measurement methods, the time-of-day of testing, and other conditions, normal response criteria should be developed in each institution. When the testing is performed for a healthy individual at around 9:00 a.m., radioimmunoassay measurement normally shows that the blood cortisol level (approximately 10 μg/mL before administration) reaches the maximum level 60 minutes after administration to 2 times the level before administration. However, when the blood cortisol level 60 minutes after administration alone is considered insufficient as the basis to determine the secretory function, it is desirable that the blood cortisol level is chronologically measured after administration to determine the secretory function.

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	Shock and anaphylaxis: Shock and anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as decreased blood pressure, angioedema, dyspnea, cough, and flushed skin are observed, appropriate measures should be adopted.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 2 months (April 2013 to June 2016). Cases related to shock and anaphylaxis: 2 case (no fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 10 000 Launched in Japan: February 1995

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 10s	Suspected of hypopituitarism (food allergy, rhinitis allergic, pituitary tumor)	100 μg for 1 day	**Anaphylaxis** ~Allergic rhinitis and food allergy~ 93 minutes before administration Blood pressure 107/71 mmHg, pulse 77/minute 15 minutes before administration An intravenous (IV) drip line was secured with a Heparin Lock for corticotropin-releasing hormone (CRH) stimulation test. The patient felt mild pain at the IV drip site; therefore, the patient was observed while resting but no change was observed. A route was secured on the opposite side and elimination of pain was confirmed. Initiate administration Administer 100 μg of this drug in 60 seconds for CRH stimulation test. 1 minute since initiation of administration While hot flashes over the whole body was confirmed, the patient was placed on observation as the flashes were considered temporary due to administration of this drug. 5 minutes after administration Occurrence of coughs, neck discomfort, and dyspnoea. Systolic blood pressure was in the 100s, $Sp0_2$ was 97% (room air), pulse rate was in the 80s, wheeze (-), and stenotic sounds in neck respiratory tract (±). Onset of anaphylaxis. 10 minutes after administration Anaphylaxis was thought to be due to administration of this drug; therefore, 500 mg hydrocortisone was administered over 30 minutes. No changes in vitals before and after administration. 15 minutes after administration Blood pressure 108/58 mmHg, pulse rate 80/minute 25 minutes after administration Blood pressure 120/59 mmHg, pulse rate 80/minute 30 minutes after administration Occurrence of right eyelid oedema. A route was secured on the opposite arm and saline solution was administered. In addition, 2L oxygen was initiated. 39 minutes after administration Blood pressure 123/61 mmHg, pulse rate 73/minute 43 minutes after administration Complaints about dyspnoea was not resolving even after administration of hydrocortisone; therefore, 0.3 mL of 0.1% adrenaline was intramuscularly administered to the lateral side of the right thigh. 47 minutes after administration Blood pressure 128/62 mmHg, pulse rate 69/minute 48 minutes after administration Symptoms of dyspnoea seemed to be resolving. 54 minutes after administration Discontinue use of oxygen. 75 minutes after administration Dyspnoea was resolved. Wheeze (-) and stenotic sounds in neck respiratory tract (-).

				84 minutes after administration Blood pressure 132/59 mmHg, pulse rate 77/minute Time unknown Patient was resolving and follow-up was performed on an outpatient basis. Anaphylaxis recovered.

Laboratory examination

Test item	5 days before administration	Day 0 of administration	Day 1 of administration
RBC ($x10^4/mm^3$)	492	-	483
WBC ($/mm^3$)	5,690	-	9,370
Neutrophil (%)	39.3	-	56.6
Eosinophil (%)	4.6	-	1.8
Basophil (%)	1.4	-	0.3
Monocyte (%)	6.5	-	7.9
Lymphocyte (%)	48.2	-	33.4
Hemoglobin content (g/dL)	14.8	-	14.3
Hematocrit (%)	42.1	-	41.1
Platelet ($x10^4/mm^3$)	17.7	-	20.8
ALP (IU/L)	419	-	357
AST (IU/L)	18	-	14
ALT (IU/L)	10	-	11
CPK (IU/L)	137	-	85
T-Bil (mg/dL)	0.57	-	0.63
Uric acid (mg/dL)	5.3	-	4.3
BUN (mg/dL)	11.1	-	7.8
Serum creatinine (mg/dL)	0.72	-	0.68
Albumin (g/dL)	4.9	-	4.1
Blood glucose (mg/dL)	119	-	102
CRP (mg/dL)	<0.01	-	0.03
Na (mEq/L)	140	-	140
K (mEq/L)	4.1	-	3.9
Cl (mEq/L)	103	-	104
Urinal sugar	negative	-	negative
Uric protein	plus-minus sign	-	negative
Urinary sediment (RBC)	negative	-	negative
Urinary sediment (WBC)	negative	-	negative
Urinary sediment (cast)	negative	-	negative
Systolic blood pressure (mmHg)	-	107	125
Diastolic blood pressure (mmHg)	-	71	55
Pulse (/min)	-	77	-
Body temperature (°C)	-	-	36.9
Heart rate (/min)	-	-	75
Respiratory rate (/min)	-	-	15
GGTP (IU/L)	-	-	9
Ca (mg/dL)	-	-	9.2

Concomitant medications: Heparin sodium

4

Revision of Precautions (No. 278)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated September 13, 2016.

1

Miscellaneous central nervous system agents

Natalizumab (genetical recombination)

Brand name	Tysabri for I.V. Infusion 300 mg (Biogen Japan Ltd)
Important precautions	Risk factors of progressive multifocal leukoencephalopathy (PML) due to this drug include being positive for anti-JC virus (JCV) Ab, having a history of treatment with an immunosuppressive agent, and long-term administration. The risk of PML is reportedly higher in patients with all these factors or those with a high anti-JCV Ab titer and a history of long-term treatment with this drug despite no history of treatment with an immunosuppressive agent. To consider the risk and benefit, the latest incidence of PML by patients with each risk factor (shown in documents such as the Guide for Proper Use) should be confirmed.
Adverse reactions (clinically significant adverse reactions)	PML, granule cell neuronopathy (GCN): PML may occur. Patients should be carefully monitored during and after treatment with this drug. If symptoms such as hemiplegia, quadriplegia, cognitive impairment, aphasia, vision disorders, and cerebellar symptoms (including ataxia and nystagmus) are observed, administration of this drug should be discontinued immediately. The onset of PML should be confirmed through examinations such as imaging diagnostics with magnetic resonance imaging and cerebrospinal fluid tests, and appropriate measures such as plasmapheresis should be adopted. In addition, cases of GCN caused by JCV have been reported in patients receiving this drug. If cerebellar symptoms occurred, potential GCN should be noted. Patients should be carefully monitored for the onset of immune reconstitution inflammatory syndrome after discontinuation of administration of the drug or after elimination of the drug by plasmapheresis.

2

Blood and body fluid agents-Miscellaneous

(1) Nartograstim (genetical recombination), (2) Filgrastim (genetical recombination) (including follow-on biologics/biosimilars), (3) Lenograstim (genetical recombination)

Brand name	(1) Neu-up injection 25 μg, 50 μg, 100 μg, 250 μg (Yakult Honsha Co., Ltd.) (2) GRAN injection 75 μg, 150 μg, GRAN injection M 300 μg, GRAN SYRINGE 75 μg, 150 μg, GRAN SYRINGE M 300 μg (Kyowa Hakko Kiri

	Co., Ltd.) and the other follow-on biologics/biosimilars (3) NEUTROGIN injection 50 μg, 100 μg, 250 μg (Chugai Pharmaceutica Co., Ltd.)
Important precautions	Complete medical histories including histories of allergies and drug hypersensitivity should be taken before initiating the therapy with this drug to predict the response of hypersensitivity, etc.
Adverse reactions (clinically significant adverse reactions)	Shock and anaphylaxis: Shock and anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

3 **Miscellaneous metabolism agents-Miscellaneous**

Pegfilgrastim (genetical recombination)

Brand name	G-LASTA Subcutaneous Injection 3.6 mg (Kyowa Hakko Kirin Co., Ltd.)
Important precautions	Complete medical histories including histories of allergies and drug hypersensitivity should be taken before initiating the therapy with this drug to predict the response of hypersensitivity, etc.

4 **Miscellaneous metabolism agents-Miscellaneous**

Eltrombopag olamine

Brand name	Revolade Tablets 12.5 mg, 25 mg (Novartis Pharma K.K.)
Precautions of dosage and administration	Blood concentration of this drug decreases when concomitantly used with products such as antacids, milk products, and formulations containing multivalent cations (iron, calcium, aluminum, magnesium, selenium, zinc, etc.). Consumption of these products should be avoided 4 hours before and 2 hours after receiving this drug.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of August 31, 2016)

◎: Products for which EPPV was initiated after August 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Lacosamide Vimpat Tablets 50 mg, 100 mg	UCB Japan Co. Ltd.	August 31, 2016
◎	Sodium Picosulfate Hydrate, Magnesium Oxide, Anhydrous Citric Acid Picoprep Combination Powder	Ferring Pharmaceuticals Co., Ltd.	August 31, 2016
◎	Carfilzomib Kyprolis Intravenous Infusions 10 mg, 40 mg	ONO Pharmaceutical Co., Ltd.	August 31, 2016
◎	Nivolumab (Genetical Recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*1]	ONO Pharmaceutical Co., Ltd.	August 26, 2016
◎	Remifentanil Hydrochloride Ultiva Intravenous 2 mg, 5 mg[*2]	Janssen Pharmaceutical K.K.	August 26, 2016
	Vigabatrin Sabril 500mg Powder	Sanofi K.K.	July 27, 2016
	Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Fumarate Genvoya Combination Tablets	Japan Tobacco Inc.	July 8, 2016
	Octocog Beta (Genetical Recombination) Kovaltry for iv injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin, Ltd.	June 29, 2016
	Bexarotene Targretin Capsules 75 mg	Minophagen Pharmaceutical Co., Ltd.	June 23, 2016
	Maxacalcitol/betamethasone butyrate propionate Marduox Ointment	Chugai Pharmaceutical Co., Ltd.	June 21, 2016
	Primaquine Phosphate Primaquine Tablets 15 mg	Sanofi K.K.	June 17, 2016
	Dutasteride (1) Zagallo Capsules 0.1 mg (2) Zagallo Capsules 0.5 mg	GlaxoSmithKline K.K.	June 13, 2016
	Mepolizumab (Genetical Recombination) Nucala for Subcutaneous Injection 100 mg	GlaxoSmithKline K.K.	June 7, 2016

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
Radium (^{223}Ra) Chloride Xofigo Injection	Bayer Yakuhin, Ltd.	June 1, 2016
Rurioctocog Alfa Pegol (Genetical Recombination) Adynovate Intravenous 250, 500, 1000, 2000	Baxalta Japan Ltd.	June 1, 2016
Trametinib Dimethyl Sulfoxide Mekinist Tablets 0.5mg, 2mg	Novartis Pharma K.K.	June 1, 2016
Dabrafenib Mesilate Tafinlar Capsules 50mg, 75mg	Novartis Pharma K.K.	June 1, 2016
Perampanel Hydrate Fycompa Tablets 2 mg, 4 mg	Eisai Co., Ltd.	May 26, 2016
Asenapine Maleate Sycrest Sublingual Tablets 5 mg, 10 mg	Meiji Seika Pharma Co., Ltd.	May 26, 2016
Sebelipase Alfa (Genetical Recombination) Kanuma Injection for Intravenous 20 mg	Alexion Pharma G.K.	May 25, 2016
Osimertinib Mesilate Tagrisso Tablets 40 mg, 80 mg	AstraZeneca K.K.	May 25, 2016
Ceritinib Zykadia Capsules 150 mg	Novartis Pharma K.K.	May 25, 2016
Ibrutinib Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	May 25, 2016
Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg*3	Teijin Pharma Limited	May 23, 2016
Botulinum Toxin Type A Botox Vista Injection 50 Units*4	Allergan Japan K.K.	May 23, 2016
Iloprost Ventavis Inhalation Solution 10 μg	Bayer Yakuhin, Ltd.	May 16, 2016
Methacholine Chloride (1) Provocholine Powder for Inhalation Solution 100 mg (2) Kenbran Powder for Inhalation Solution 100 mg	(1) Sanwa Kagaku Kenkyusho Co., Ltd. (2) Santen Pharmaceutical Co., Ltd.	May 10, 2016
Nonacog Gamma (Genetical Recombination) Rixubis Intravenous 250, 500, 1000, 2000, 3000	Baxter Limited	May 9, 2016
Luliconazole Luconac Solution 5% *5	Sato Pharmaceutical Co., Ltd.	April 25, 2016
Progesterone Luteum Vaginal Suppository 400 mg	Aska Pharmaceutical Co., Ltd.	April 21, 2016
Evolocumab (Genetical Recombination) Repatha SC Injection 140 mg syringe, 140 mg pen	Amgen Astellas BioPharma K.K.	April 21, 2016
Ibandronate Sodium Hydrate Bonviva Tablets 100 mg	Chugai Pharmaceutical Co., Ltd.	April 21, 2016
Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg *6	Shionogi & Co., Ltd.	March 18, 2016

*1 Radically unresectable or metastatic renal cell carcinoma

*2 Analgesia in maintaining general anesthesia of children

*3 Hyperuricemia associated with cancer chemotherapy

*4 Lateral canthal lines in adult patients under the age of 65
*5 Nail tinea
*6 Pain associated with chronic lumbago