Pharmaceuticals and Medical Devices Safety Information

No. 319 December 2014

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).

Published by
Ministry of Health, Labour and Welfare

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

Pharmaceuticals and Medical Devices Safety Information

No. 319 December 2014

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

[Outline of Information]

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

PMDA medi-navi
(Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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

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

Abbreviations

ADR	Adverse Drug Reaction
DIHS	Drug-Induced Hypersensitivity Syndrome
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
JIMGA	Japan Industrial and Medical Gases Association
LTOT	Long-Term Oxygen Therapy
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
OTC	Over-the-Counter
PMDA	Pharmaceuticals and Medical Devices Agency

1

Summary of the Relief System for Sufferers from Adverse Drug Reactions and the Cases of Non-payment of Relief Benefits Due to Improper Use of Drugs

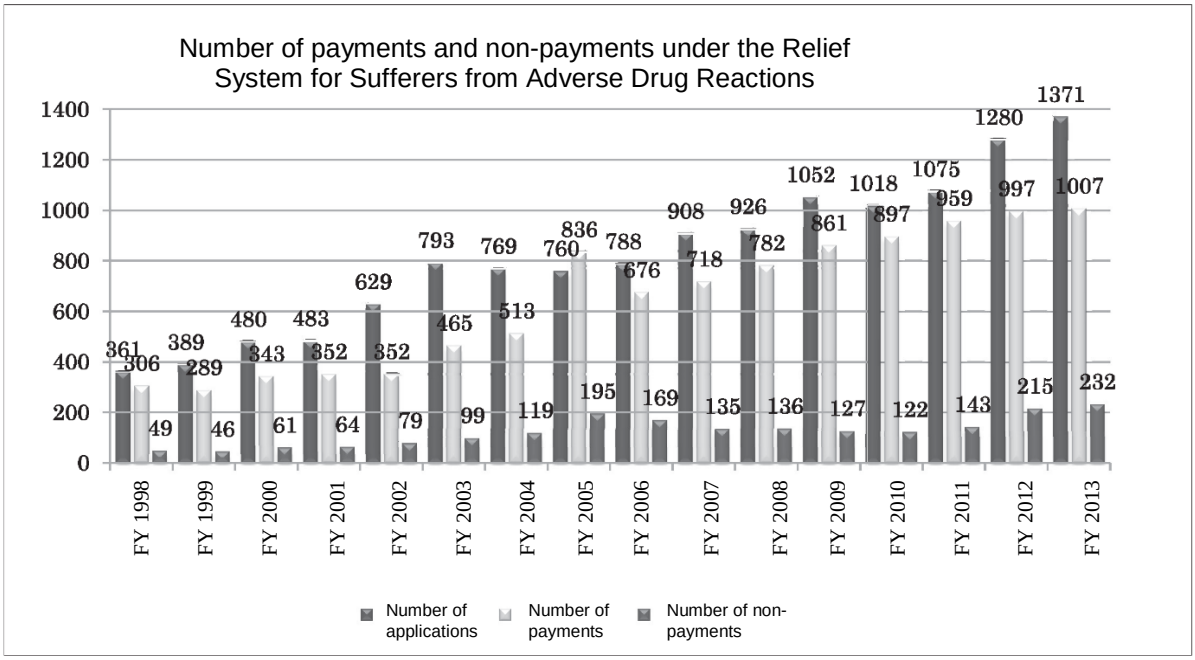
1. Introduction

The Relief System for Sufferers from Adverse Drug Reaction (ADR) (hereinafter referred to as "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 (including over-the-counter [OTC] drugs), despite using them properly. This is a public service funded by contributions from marketing authorization holders (MAHs) of pharmaceuticals as a way to fulfill some of their social responsibilities.

As shown in **Figure 1**, the number of applications for the Relief System and payments of relief benefits has been increasing in recent years. Since the establishment of the Relief System in 1980 until the end of fiscal year (FY) 2013, over 15 000 persons were granted relief benefits. However, the Relief System is recognized by only 21.2% of Japanese people in general; 4.9% of those surveyed answered they knew the system and 16.3% answered they have heard about the system.[Note 1)] It is inferred that some people may not file an application for compensation for the adverse health effects associated with ADR they have suffered because they don't know about the Relief System. Healthcare professionals are encouraged to provide the information on the Relief System to patients or their families for utilization of the Relief System if such adverse health effects occur. Your cooperation in preparation of medical certificates to help patients filing an application would be appreciated.

Note 1) 2013 Awareness Survey on the Relief System for Sufferers from ADR
http://www.pmda.go.jp/kenkouhigai/ninchi/h25_ninchi_gaiyo.html
(only available in Japanese language)

Figure 1 Number of relief benefits from the Relief System



* A second claim for the same cause was counted.
* Number of applications and total number of payments and non-payments made in the FY are not consistent since a certain period is required from the receipt of the applications to the decision on benefit payments.

For a similar system for biological products, the Relief System for Sufferers from Disease Infected from Biological Products was established in 2004 to bring prompt relief to people who suffered from adverse health effects such as disorders or diseases caused by viral infections from viruses etc., despite using biological products properly. As of the end of FY 2013, 46 persons have been granted relief benefits.

In addition, adverse reactions and infections associated with regenerative medical products also started to be covered by the Relief System on November 25, 2014.

2. Summary of adverse reaction relief benefits

Adverse health effects subject to adverse reaction relief benefits include disorders (requiring admission), disabilities (significantly activity limitation during daily life), and deaths despite properly using drugs or regenerative medical products (hereinafter referred to as pharmaceuticals). Pharmaceuticals referred to in the Relief System include all pharmaceuticals approved by the Minister of Health, Labour and Welfare (MHLW). While pharmaceuticals prescribed or used at hospitals and clinics and those purchased at pharmacies are all subject to relief benefits, some pharmaceuticals such as anticancer drugs and immunosuppressants are not.

A summary of ADR relief benefits made by the Relief System is shown below (as of April 1, 2014). For details of the system, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai/help/benefit.html [only available in Japanese language]).

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

- Compensation will reflect actual costs of treatment for diseases caused by ADR.

Medical Allowance (33 200 to 35 200 yen per month)

- Benefits are provided for costs other than medical costs for treatment of disorders caused by ADR.

Disability Pension (Grade 1, 2 672 400 yen per year; Grade 2, 2 138 400 yen per year)

- Benefits are provided to compensate for living costs etc., of patients aged 18 or older, who suffer from a certain degree of disability caused by ADR.

Pension for Raising Children with disabilities (Grade 1, 835 200 yen per year; Grade 2, 668 400 yen per year)

- Benefits are provided for people who are responsible for raising children under 18 years old who suffer from a certain degree of disability caused by ADR.

Bereaved Family Pension (2 337 600 yen per year for 10 years)

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

Lump-sum Allowances for Bereaved Family (7 012 800 yen)

- Benefits are provided for bereaved families for condolence and sympathy following the death from ADR of their family member who is not the main provider.

Funeral Expenses (206 000 yen)

- Benefits are provided for the costs of holding a funeral for the person who died from ADR.

[Cases of relief benefit payments]

<Case 1>

After orally taking a common cold drug (OTC drugs) to relieve cold symptoms, the patient had toxic epidermal necrolysis and was admitted to hospital for treatment for 15 days. Medical Expenses and Medical Allowance were paid.

<Case 2>

After using iodine contrast media, the patient had anaphylactoid shock followed by hypoxic encephalopathy and was left with severe brain dysfunction. Disability Pension was paid.

<Case 3>

After orally taking methotrexate capsules for treatment of rheumatoid arthritis, the patient had interstitial pneumonia and was admitted to hospital for treatment for approximately 2 months, but died. Medical Expenses, Medical Allowance, Bereaved Family Pension, and Funeral Expenses were paid.

3. Information on the Relief System

For details of the Relief System and the Relief System for Sufferers from Disease Infected from Biological Products, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai.html [only available in Japanese language]). The following materials are also available on the PMDA website (only available in Japanese language). Promotion of the Relief System using these materials is encouraged.

- Booklet describing a clear explanation of the Relief System (for healthcare professionals)
  Important to know. Important to inform. Relief System for Sufferers from ADR
  http://www.pmda.go.jp/kenkouhigai/file/higaikyusai.pdf
- Leaflet on the Relief System
  Relief System for Sufferers from ADR
  http://www.pmda.go.jp/kenkouhigai/ldp/file/fukusayo_leaflet.pdf
  Relief System for Sufferers from Disease Infected from Biological Products
  http://www.pmda.go.jp/kenkouhigai/ldp/file/seibutuyurai.pdf
- Poster for Relief System for Sufferers from ADR
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_keiji.pdf

- Materials for medication bag
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_kusuri.pdf

A consultation service is available (including the Relief System for Sufferers from Disease Infected from Biological Products):

- Relief System Consultation Service, PMDA
  Phone: 0120-149-931 (toll-free)
  Office hours: Monday to Friday 9:00-17:00 (excluding national holidays and New Year holidays)
  E-mail：kyufu@pmda.go.jp

Caution should be paid to the cases not applicable for relief benefits as shown below.

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 Preventive Vaccination Law). However, cases of adverse health effects resulting from voluntary vaccinations are applicable for relief benefits under the Relief System for Sufferers.
b. Cases where it is clear who is responsible for adverse health effects, including the case of product liability of the MAHs of the pharmaceuticals.
c. Cases where it is necessary to use the pharmaceuticals 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.
d. Cases where it is not confirmed that the pharmaceuticals are used for the proper purpose and with the proper method.
   (e.g., cases where the pharmaceuticals have been used in ways other than indications approved by the Minister of Health, Labour and Welfare, or cases where the pharmaceuticals have not been used in accordance with the Precautions section in the package inserts)
e. Cases of adverse health effects caused by pharmaceuticals inapplicable for the relief benefits.
   Pharmaceuticals inapplicable for the relief benefits:
   (1) Pharmaceuticals used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
   (2) Pharmaceuticals that do not have the possibility to cause adverse reactions, 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 or treatment equivalent to inpatient care is not required) or cases where disabilities caused by pharmaceuticals fail to meet the disability criteria under the Relief Systems[Note)].
   Note) 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)"
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 MHLW based on medical and pharmaceutical judgment.
   - Cases where the disorders or disabilities are considered to be unlikely caused by ADR (those that are not considered to be associated with pharmaceuticals).
   - Cases where it cannot be judged whether there are causalities or whether pharmaceuticals are used for the proper purpose and with the proper method, because of insufficient documentation (impossible to judge).

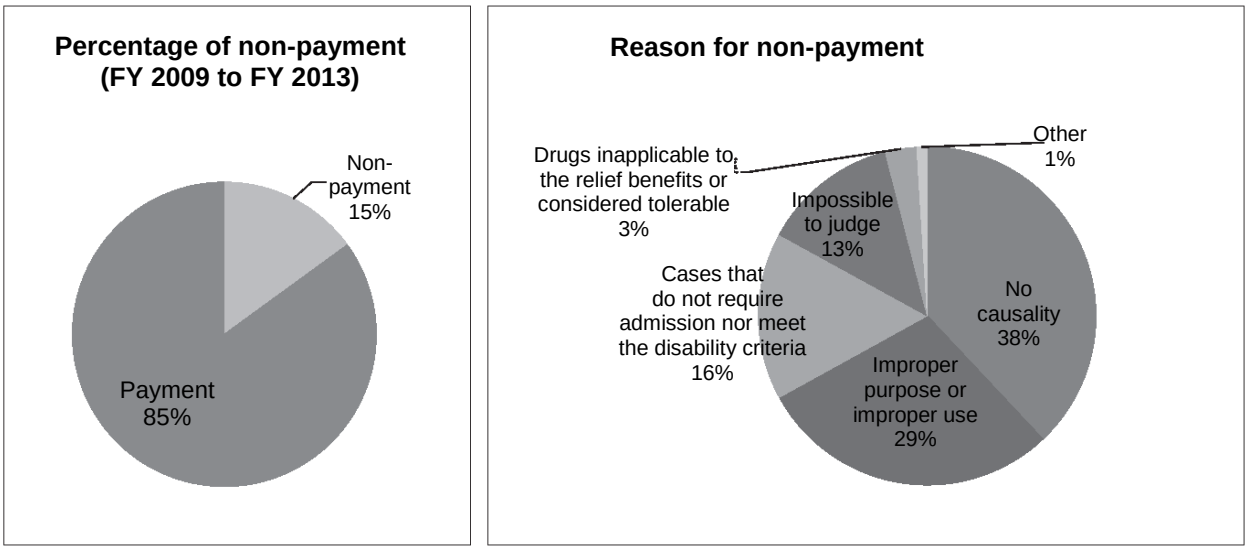
4. Summary of payment/non-payment cases in the Relief System

Between FY 2009 and FY 2013, the percentage of payments and non-payments was 85% and 15%, respectively. Details of adverse health effects associated with pharmaceuticals among cases receiving payments and reasons for non-payments are shown in **Figure 2**.

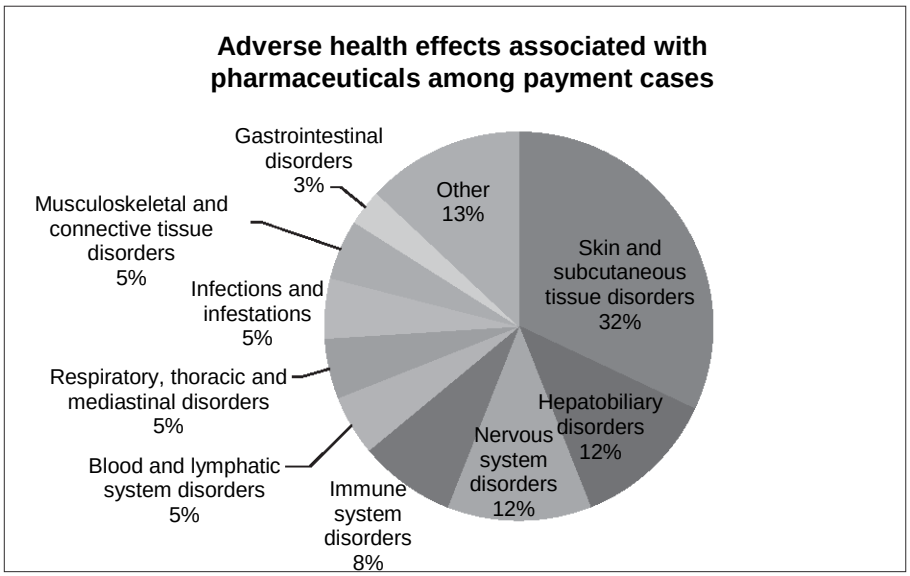
The goal of standard administrative processing time from when the PMDA receives an application to when the PMDA notifies the applicant of the decision[Note 2)] was within 6 months in 60% or more and within 8 months in 70% or more of cases for which payment or non-payment was determined. The actual achievement percentage in FY 2013 was 60.8% and 85.7%, respectively.

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 2 Percentage of payments and non-payments with details of adverse health effects and reasons for non-payments between FY 2009 and FY 2013



Reason for non-payment for a total of 839 cases which were determined not to receive payments among all 5 570 claims between FY 2009 and FY 2013



A total of 6 388 adverse health effects associated with pharmaceuticals are summarized by MedDRA/J System Organ Class based on 4 721 cases which were determined to receive payments between FY 2009 and FY 2013

5. Cases where it is not confirmed that the pharmaceuticals are used with the proper method

In 29% of 839 non-payment cases between FY 2009 and FY 2013[Note 3)], the reason for non-payments was that the purpose or method of use of pharmaceuticals was not considered proper.

The reasons why the method of use was not considered proper in the most recent years (longer than one year) are presented here, together with the description in package inserts or specific cases.

Note 3) Number of claimants: a second claim for the same cause was counted.

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

Cases where the method of use of a drug is not considered proper because the drugs were used in ways other than the approved dosage and administration are presented here. This is the most common reason why the use of a drug is not considered proper, and cases using lamotrigine account for a large majority of those cases.

Healthcare professionals should pay attention to the dosage and administration when using pharmaceuticals.

Case 1 Severe drug eruption associated with lamotrigine

In cases of severe drug eruption associated with lamotrigine (Lamictal tablets), there are still many cases in which the use was considered improper and no payment was made. Most of the cases involved administration of more than the recommended initial dosage and noncompliance with dose increase intervals. Dosage and administration of lamotrigine are spelled out for specific indications and concomitant pharmaceuticals. Healthcare professionals should carefully read the package insert, especially the Precautions of Dosage and Administration section describing a high incidence of skin disorders such as rash when lamotrigine is used at an excessive dose.

Case 2 Gastric perforation associated with diclofenac sodium sustained-release capsules

Diclofenac sodium sustained-release capsules (Voltaren SR) were used for one capsule per dose, three times a day, for approximately 4 months, resulting in gastric perforation.

Dosage and Administration

The usual adult dosage is 37.5 mg/dose (as diclofenac sodium) administered twice a day after a meal.

(2) Cases where necessary tests are not performed

After (1), the next most common reason why the method of use is not considered proper was cases where necessary tests specified in the package insert had not been performed. This documents have been provided precautions to healthcare professionals about relatively commonly reported “agranulocytosis associated with thiamazole (Mercazole),” “agranulocytosis and drug-induced liver injury associated with ticlopidine hydrochloride (ex. Panaldine),” “fulminant hepatitis associated with benzbromarone (ex. Urinorm),” “agranulocytosis associated with salazosulfapyridine (ex. Azulfidine),” “lithium poisoning associated with lithium carbonate (ex. Limas),” etc. This time, cases where the method of use is not considered proper other than the above are presented.

Appropriate tests should be performed to ensure early detection of ADR and avoid symptom aggravation. Healthcare professionals should pay attention to the Precautions section of the package insert to ensure proper use of the drug.

Case 1 Hyperosmolar hyperglycaemic syndrome associated with quetiapine fumarate

After measuring blood glucose level, etc. before the start of administration of quetiapine fumarate (Seroquel tablets), hyperosmolar hyperglycaemic syndrome occurred without periodic monitoring for blood glucose level.

Warnings

(1) A marked increase in blood glucose level may cause clinically significant adverse reactions such as diabetic ketoacidosis and diabetic coma, leading to fatal outcome in some cases. During treatment with this drug, patients should be carefully monitored by checking blood glucose level.

(2) Prior to treatment with this drug, patients and their families should be thoroughly informed of possible occurrence of the above adverse reactions. They also should be instructed to watch for abnormalities such as thirst, excessive drinking, polyuria, and pollakiuria, and to discontinue this drug and consult their physician immediately if such symptoms occur.

Case 2 Hypercalcaemia associated with eldecalcitol

Serum calcium level was never measured until hypercalcaemia was found 1 year and 4 months after the start of treatment with eldecalcitol (Edirol capsules), and the use was continued for 2 months and a half even after marked renal disorder was found.

Important Precautions

During treatment with this drug, serum calcium level should be measured periodically (approximately once in 3-6 months), and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken. Particular attention should be paid by frequently measuring serum calcium level at an early stage of treatment in patients who have hypercalcaemia risk such as renal impairment, malignant tumor, and primary hyperparathyroidism.

Clinically Significant Adverse Reactions

Acute renal failure: Acute renal failure with an elevation in serum calcium may occur. Serum calcium level and renal function should be periodically monitored and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

(3) Cases where the pharmaceuticals were used in noncompliance with contraindications

In some cases considered as improper drug use, the drug was used in a patient to whom it was contraindicated.

Healthcare professionals should consider proper use of the drug by thoroughly reviewing the patient's underlying disorders, complications, past allergies, past adverse reactions, past medications used at other hospitals, etc.

Case 1 Use of mesalazine tablets in a patient with a past history of hypersensitivity to mesalazine

A patient with a history of drug-induced eosinophilic pneumonia suggestively caused by mesalazine (Pentasa tablets) was treated with Asacol tablets containing the same ingredient, resulting in interstitial pneumonia.

Contraindication

Patients with a history of hypersensitivity to ingredients of this drug (Asacol tablets)

Case 2 Use of fosphenytoin sodium in a patient with a past history of hypersensitivity to hydantoin compounds

Pyrexia, rash, etc. were observed during treatment with phenytoin tablets, and consequently administration of this drug was discontinued. After that, fosphenytoin sodium was intravenously

administered, resulting in drug-induced hypersensitivity syndrome (DIHS).

Important Precaution

Patients with hypersensitivity to ingredients of this drug or hydantoin compounds (Fostoin injection)

(4) Cases where patients take the drug by self-judgment not based on the instructions of physicians

Cases where an ethical drug prescribed by a physician was used based on the patient's self-judgment without instructions of physicians or where an ethical drug prescribed to a family member or a friend was used were considered to be cases where it is not confirmed that the pharmaceuticals are used for the proper purpose and with the proper method.

Healthcare professionals are encouraged further to help patients properly use pharmaceuticals by specifically advising patients about the optimal timing and dosage.

Case 1 Use of a drug prescribed for cold symptoms by self-judgment

The patient had cold symptoms, took, by self-judgment, the remaining portions of a common cold drugs and carbocysteine tablets which were prescribed by a physician approximately 9 months ago, and subsequently had erythema multiforme-type drug eruption.

Case 2 Use of a drug by self-judgment even after a physician gave instructions to discontinue the drug

The patient took, by self-judgment, carbamazepine tablets even after a physician gave instructions to discontinue the drug, and subsequently had DIHS.

(5) Other cases where the pharmaceuticals were used in noncompliance with the package insert descriptions

In cases where a drug was continuously used despite descriptions of precautions such as discontinuation of use in the package insert, the method of use was not considered proper. Healthcare professionals should check again the descriptions in package inserts.

Case 1 Osteomyelitis and osteonecrosis associated with bisphosphonates

Approximately 4 years after the start of treatment with alendronate tablets, the patient received dental treatment due to gingival swelling. Exposure of tooth root and looseness of a tooth were observed, and tooth extraction was performed. After that, having noticed an abnormality in the skin of the lower right jaw, the patient visited the prescribing medical institution. The patient told the prescribing physician about the abnormality of gingiva that occurred after the start of treatment with alendronate tablets and the subsequent clinical course related to tooth extraction. The prescribing physician also recognized the redness and swelling of the lower right jaw as a dental-related infection, and perceived risk factors and signs related to osteomyelitis and osteonecrosis of jawbone associated with alendronate tablets. However treatment with this drug was continued until the occurrence of external dental fistula.

Important Precautions

Osteonecrosis or osteomyelitis of the jaw may occur in patients treated with bisphosphonates including this drug. In most reported cases, the events occurred in association with invasive dental procedures in the jaw bone, such as tooth extraction, or local infection. Known risk factors include malignant tumor, chemotherapy, corticosteroid therapy, radiotherapy, poor oral hygiene, and past dental procedures. Before using this drug, the status of oral care management should be checked. If necessary, patients should be instructed to receive an appropriate dental examination and to have invasive dental procedures be finished before treatment as much as possible. If invasive dental procedures are required during administration of this drug, suspension of this drug should be considered.

In addition, patients should be thoroughly informed of the importance of oral hygiene, receiving periodic dental examinations, notifying his/her dentist about use of this drug to avoid invasive dental procedures as much as possible. Patients also should be advised to see a dentist/oral surgeon, if any abnormalities occur.

Case 2 Generalized drug eruption associated with carbamazepine

The patient had drug eruption after taking carbamazepine tablets and visited the dermatology department 6 days after the onset, but the treatment was continued for 8 days after that.

Clinically Significant Adverse Reactions

Toxic epidermal necrolysis, oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, erythroderma (exfoliative dermatitis): Serious skin symptoms may occur. Patients should be carefully observed, if abnormalities such as pyrexia, ocular hyperaemia, face swelling, erosion of lip/oral mucosa or genital area, blisters on the skin or mucosa, many small pustules, erythema, pharynx pain, itching, general malaise are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

6. Closing comments

Healthcare professionals are encouraged to thoroughly read the package inserts before using pharmaceuticals and to use them properly. Please note that the cases where pharmaceuticals are not used properly may not be applicable for the relief benefits under public relief systems, even though the adverse health effects are suspected to have been caused by pharmaceuticals.

When adverse reactions occur and healthcare professionals are consulted by their patient about the reactions, the healthcare professionals should provide information regarding the Relief Systems to the patient or their family, if the reactions are possibly applicable for the relief benefits. MHLW/PMDA hopes for your particular cooperation in preparing the documents, such as a medical certificate required to claim these relief benefits.

2

Revision of Precautions (No. 261)

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 November 20, 2014.

1

Central nervous system agents-Miscellaneous

Galantamine Hydrobromide

Brand Name	Reminyl Tablets 4 mg, 8 mg, and 12 mg, Reminyl OD Tablets 4 mg, 8 mg, and 12 mg, and Reminyl Oral Solution 4 mg/mL (Janssen Pharmaceutical K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Acute generalised exanthematous pustulosis:** Acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities such as pyrexia, erythema, and many small pustules are observed, administration of this drug should be discontinued and appropriate measures should be taken.

3

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 the 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 December 1, 2014)

◎: Products for which EPPV was initiated after November 2, 2014

	Nonproprietary name / Brand name on	Name of the MAH	Date of EPPV initiate
◎	pegfilgrastim (genetical recombination) G-lasta Subcutaneous Injection 3.6 mg	Kyowa Hakko Kirin Co., Ltd.	November 28, 2014
◎	suvorexant Belsomra Tablets 15 mg, 20 mg	MSD K.K.	November 26, 2014
◎	vaniprevir Vanihep Capsules 150 mg	MSD K.K.	November 25, 2014
◎	anagrelide hydrochloride hydrate Agrylin Capsules 0.5 mg	Shire Japan KK	November 25, 2014
◎	tiotropium bromide hydrate Spiriva 2.5 μg Respimat 60 puffs*[1]	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2014
◎	aflibercept (genetical recombination) Eylea Solution Intravitreal Injections 40 mg/mL, Eylea Solution Intravitreal Injections Kit 40 mg/mL*[2]	Bayer Yakuhin, Ltd.	November 18, 2014
◎	Freeze-dried activated human blood coagulation factor VII concentrate containing factor X Byclot for Intravenous Injection	The Chemo-Sero-Therapeutic Research Institute	November 11, 2014
	standardized Japanese cedar pollen extract original solution Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL bottle, 2 000 JAU/mL bottle, 2 000 JAU/mL pack	Torii Pharmaceutical Co., Ltd.	October 8, 2014
	bimatoprost GlashVista Cutaneous Solution 0.03% 5 mL	Allergan Japan K.K.	September 29, 2014
	edoxaban tosilate hydrate Lixiana Tablets 15 mg, 30 mg*[3]	Daiichi Sankyo Company, Limited	September 26, 2014
	voriconazole Vfend Tablets 50 mg, 200 mg, Vfend for Intravenous Use 200 mg*[4]	Pfizer Japan Inc.	September 26, 2014
	metronidazole Anaemetro Intravenous Infusion 500 mg	Pfizer Japan Inc.	September 26, 2014
	delamanid Deltyba Tablets 50 mg	Otsuka Pharmaceutical Co., Ltd.	September 26, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
treprostinil Treprost 20 mg for Injection, 50 mg for Injection, 100 mg for Injection, 200 mg for Injection	Mochida Pharmaceutical Co., Ltd.	September 26, 2014
anti-human thymocyte immunoglobulin, rabbit Thymoglobuline for Intravenous Infusions 25 mg*5	Sanofi K.K.	September 19, 2014
donepezil hydrochloride Aricept Tablets 3 mg, 5 mg, 10 mg, Aricept D Tablets 3 mg, 5 mg, 10 mg, Aricept Fine Granules 0.5%, Aricept Oral Jelly 3mg, 5mg, 10 mg, Aricept Dry Syrup 1%*6	Eisai Co., Ltd.	September 19, 2014
aflibercept (genetical recombination) Eylea Solution for IVT inj. 40mg/mL, Eylea Solution for IVT inj. Kit 40 mg/mL*7	Bayer Yakuhin, Ltd.	September 19, 2014
calcipotriol hydrate/betamethasone dipropionate Dovobet Ointment	Leo Pharma K.K.	September 12, 2014
eftrenonacog alfa (genetical recombination) Alprolix Intravenous 500, 1000, 2000, 3000	Biogen Idec Japan Ltd.	September 8, 2014
alectinib hydrochloride Alecensa Capsules 20 mg, 40 mg	Chugai Pharmaceutical Co., Ltd.	September 5, 2014
cabazitaxel acetonate Jevtana 60 mg I.V. Infusion	Sanofi K.K.	September 4, 2014
umeclidinium bromide/vilanterol trifenatate Anoro Ellipta 7 doses	GlaxoSmithKline K.K.	September 4, 2014
(1) daclatasvir hydrochloride (2) asunaprevir (1) Daklinza Tablets 60 mg (2) Sunvepra Capsules 100 mg	Bristol-Myers K.K.	September 3, 2014
cysteamine bitartrate Nicystagon Capsules 50 mg, 150 mg	Mylan Seiyaku Ltd.	September 3, 2014
canagliflozin hydrate Canaglu Tablets 100 mg	Mitsubishi Tanabe Pharma Corporation	September 3, 2014
nivolumab (genetical recombination) Opdivo Intravenous Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	September 2, 2014
ruxolitinib phosphate Jakavi Tablets 5 mg	Novartis Pharma K.K.	September 2, 2014
velaglucerase alfa (genetical recombination) Vpriv Intravenous Injection 400 U	Shire Japan KK	September 2, 2014
abiraterone acetate Zytiga Tablets 250 mg	Janssen Pharmaceutical K.K.	September 2, 2014
efinaconazole Clenafin Topical Solution 10% for Nail	Kaken Pharmaceutical Co., Ltd.	September 2, 2014
rituximab (genetical recombination) Rituxan Injection 10 mg/mL*8	Zenyaku Kogyo Co., Ltd.	August 29, 2014
phenothrin Sumithrin Lotion 5%	Kracie Pharma, Ltd.	August 22, 2014
tapentadol hydrochloride Tapenta Tablets 25 mg, 50 mg, 100 mg	Janssen Pharmaceutical K.K.	August 18, 2014

Nonproprietary name / Brand name on		Name of the MAH	Date of EPPV initiate
	fentanyl citrate	Hisamitsu Pharmaceutical Co., Inc.	June 20, 2014
	Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg*9		
	sorafenib tosilate	Bayer Yakuhin, Ltd.	June 20, 2014
	Nexavar Tablets 200 mg*10		
	pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein)	Pfizer Japan Inc.	June 20, 2014
	Prevenar 13 Suspension Liquid for Injections*11		
	azilsartan/amlodipine besilate	Takeda Pharmaceutical Company Limited	June 18, 2014
	Zacras Combination Tablets LD, HD		
	natalizumab (genetical recombination)	Biogen Idec Japan Ltd.	June 4, 2014
	Tysabri. for I.V. Infusions 300 mg		

*1 An additional indication for “the remission of various symptoms associated with airway obstructive disorder in patients with the following diseases: bronchial asthma (to be used only in patients with severe and persistent disease)”

*2 An additional indication for “the treatment of patients with diabetic macular oedema”

*3 An additional indication for “the reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and the treatment and suppression of relapse for venous thromboembolisms (deep vein thrombosis and pulmonary thromboembolism)”

*4 An additional administration for “pediatrics”

*5 An additional indication for “the treatment of acute rejection after transplantation of heart, lung, liver, pancreas, and small intestine”

*6 An additional indication for “the suppression of progression of dimentia symptoms in patients with Lewy body dementia”

*7 An additional indication for “the treatment of choroidal neovascularization in pathologic myopia”

*8 An additional indication for “the treatment of patients with refractory nephrotic syndrome (frequently relapsing or steroid-resistant)”

*9 An additional indication for “the treatment of moderate to severe chronic pain”

*10 An additional indication for “the treatment of patients with radically unresectable differentiated thyroid carcinoma”

*11 An additional indication for “the prevention of infection caused by Streptococcus pneumonia serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in geriatrics”

Handling of Fire during Long-term Oxygen Therapy

1. Introduction

Long-term oxygen therapy (LTOT) is an at-home treatment for chronic respiratory failure patients to inhale highly-concentrated oxygen by using an oxygen concentrator, liquid oxygen units, and oxygen cylinders (hereinafter referred to as an "oxygen concentrator").

The oxygen concentrator can be used safely when properly used in accordance with the instructions in the package insert and the user's manual. Since oxygen is a combustion-enhancing gas, however, sources of fire should be handled with the utmost care. The package insert and the user's manual contain precautions not to put any sources of fire close to the oxygen concentrator. Moreover, the MHLW and the Japan Industrial and Medical Gases Association (JIMGA) have prepared and distributed leaflets and videos for handling of fire during LTOT to alert patients and their families.

However, fatal fire accidents believed to be caused by smoking, etc. have still occurred repeatedly in patients using LTOT. Accordingly, healthcare professionals, patients, and their families are advised again to take thorough precautions.

Table 1 shows Cases of serious health damage due to fire in the houses of patients using LTOT for which information was updated as of the end of November 2014 by the JIMGA.

2. Request for taking thorough safety measures

As the MHLW and the JIMGA have issued an alert against fire accidents, patients using LTOT and their families need to take the following precautions against handling of fire when using the oxygen concentrator. Healthcare professionals are advised again to thoroughly alert patients and their families.

1) Sources of fire, including smoking near an oxygen concentrator while using LTOT, may cause items such as cannulas and clothing to ignite, resulting in severe burn injuries or house fires.

2) Any sources of fire should not be put within 2 meters of an oxygen concentrator.

   Smoking is strictly prohibited especially while using LTOT.

3) Oxygen will not cause items such as cannulas and clothing to ignite or cause home fires when properly used in accordance with the user's manual and appropriate precautions against fire. You are advised to use oxygen therapy in accordance with the instructions given by the doctor without being unduly afraid.

<References>

1. MHLW: Handling of Fire during LTOT
   http://www.mhlw.go.jp/stf/houdou/2r98520000003m15_1.html (only available Japanese language)
2. Cases of serious health damage due to fire in the houses of patients using LTOT (JIMGA)
   http://www2.jimga.or.jp/dl/iryo/all/top/HOT_jiko.pdf (only available Japanese language)
3. Precautions against Handling of Fire during LTOT (JIMGA)
   http://www.jimga.or.jp/front/bin/ptlist.phtml?Category=7041 (only available Japanese language)

Table 1 Cases of serious health damage due to fire in the houses of patients using LTOT (Prepared by JIMGA [as of the end of November, 2014])

No.	Date of occurrence	Location (Prefecture)	Age (sex)	Health damage	Cause (including suspected cause)
1	December 2003	Shizuoka	70s (M)	Death (by fire)	Smoking
2	May 2004	Tokyo	80s (F)	Death	(Unknown; fire origin, kitchen)
3	February 2005	Tochigi	70s (M)	Death	Smoking
4	March 2005	Hiroshima	60s (M)	Death (by fire)	Smoking (in bed)
5	March 2005	Fukushima	80s (M)	Death (by fire)	Current leakage (electric blanket)
6	July 2005	Hyogo	60s (M)	Death (by fire)	Smoking
7	November 2005	Hiroshima	70s (M)	Death (by fire)	(Unknown; smoking in bed)
8	March 2006	Okayama	80s (M)	Death (by fire)	(Unknown)
9	May 2006	Tokyo	80s (M)	Death (burn injury)	Cigarette not put out properly
10	August 2006	Kyoto	80s (F)	Death (CO intoxication)	Smoking (in bed)
11	August 2006	Hyogo	60s (F)	Serious injury (burn injury) → Death	Smoking
12	October 2006	Kyoto	70s (M)	Death (by fire)	Smoking
13	December 2006	Kyoto	10s (F)	Death	Space heater
14	March 2007	Nagano	50s (M)	Death (by fire)	Smoking
15	March 2007	Aichi	40s (M)	Death (by fire)	(Unknown)
16	April 2007	Chiba	60s (M)	Death (by fire)	(Unknown)
17	May 2007	Hyogo	80s (F)	Serious injury (burn injury of the face)	Smoking
18	November 2007	Fukushima	80s (M)	Death	Smoking
19	December 2007	Tokyo	80s (F)	Death	(Unknown; fire origin, kitchen)
20	March 2008	Yamaguchi	70s (F)	Death	Smoking
21	November 2008	Tokyo	70s (M)	Death	Ignition of incense with a lighter
22	January 2009	Nara	≥ 90 (M)	Death (by fire)	Space heater
23	February 2009	Kagoshima	50s (M)	Death (by fire)	Smoking
24	March 2009	Chiba	80s (M)	Death (by fire)	Space heater or family altar
25	May 2009	Saitama	70s (F)	Death (by fire)	(Unknown; fire origin, near the power source)
26	October 2009	Kyoto	80s (M)	Death (by fire)	Smoking
27	November 2009	Hyogo	60s (F)	Death (by fire)	(Unknown)
28	December 2009	Tokyo	70s (M)	Serious injury (burn injury) → Death	(Unknown)
29	January 2010	Osaka	80s (M)	Serious injury (burn injury) → Death	Smoking
30	September 2010	Kanagawa	60s (M)	Death (by fire)	(Unknown; cigarette not put out properly?)
31	September 2010	Tokyo	70s (M)	Death (by fire)	(Unknown; non-smoker)
32	November 2010	Tokushima	80s (M)	Death (by fire)	(Unknown)
33	January 2011	Osaka	40s (F)	Death	(Unknown; smoking?)
34	January 2011	Hyogo	80s (M)	Death (by fire)	(Unknown)
35	April 2011	Nagano	70s (F)	Death (by fire)	Cigarette not put out properly
36	April 2011	Okayama	60s (M)	Death (by fire)	Cigarette not put out properly
37	September 2011	Wakayama	70s (M)	Death (by fire)	(Unknown; lighted candle?)
38	June 2012	Okayama	80s (M)	Death	Smoking
39	November 2012	Kyoto	70s (F)	Death (by fire)	(Unknown: space heater?)
40	November 2012	Osaka	60s (M)	Death (by fire)	(Unknown; smoking?)
41	March 2013	Fukuoka	80s (M)	Death (by fire)	(Unknown)
42	August 2013	Okinawa	70s (M)	Severe (burn injury in airway)	(Unknown)
43	November 2013	Niigata	80s (F)	Death (by fire)	(Unknown: space heater?)
44	November 2013	Yamagata	70s (M)	Death (by fire)	(Unknown)
45	December 2013	Osaka	80s (F)	Death	(Unknown)
46	January 2014	Saitama	80s (M)	Death (by fire)	Current leakage
47	January 2014	Gifu	60s (F)	Death (by fire)	Current leakage
48	January 2014	Akita	70s (M)	Death (by fire)	(Unknown: space heater?)
49	April 2014	Nagano	70s (M)	Death	(Unknown)
50	May 2014	Aichi	70s (M)	Death (by fire)	(Unknown)
51	August 2014	Osaka	80s (F)	Death	Smoking
52	October 2014	Tokyo	70s (M)	Death	Smoking