Pharmaceuticals and Medical Devices Safety Information

No. 307 November 2013

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).

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Pharmaceuticals and Medical Devices Safety Information
No. 307 November 2013

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

5-FU	5-fluorouracil
ADAMTS 13	A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13
ADRs	Adverse drug reactions
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
bpm	beats per minute
BUN	Blood urea nitrogen
CAG	Coronary angiography
CK	Creatine kinase
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FOLFIRI	5-fluorouracil/leucovorin plus irinotecan
FY	Fiscal year
Hb	Hemoglobin
Ht	Hematocrit
ICU	Intensive care unit
IFNa	Interferon alfa
IU	International unit
IVH	Intravenous hyperalimentation
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	5-fluorouracil/leucovorin plus oxaliplatin
OTC	Over-the-counter drug
PLT	Platelet
PS	Performance status
RBC	Red blood cell count
sLV5FU	5-fluorouracil/leucovorin
SpO_2	Oxygen saturation
T-Bill	Total bilirubin
TEN	Toxic epidermal necrolysis
TMN	Tumour-metastasis-node
TTP	Thrombotic thrombocytopenic purpura
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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

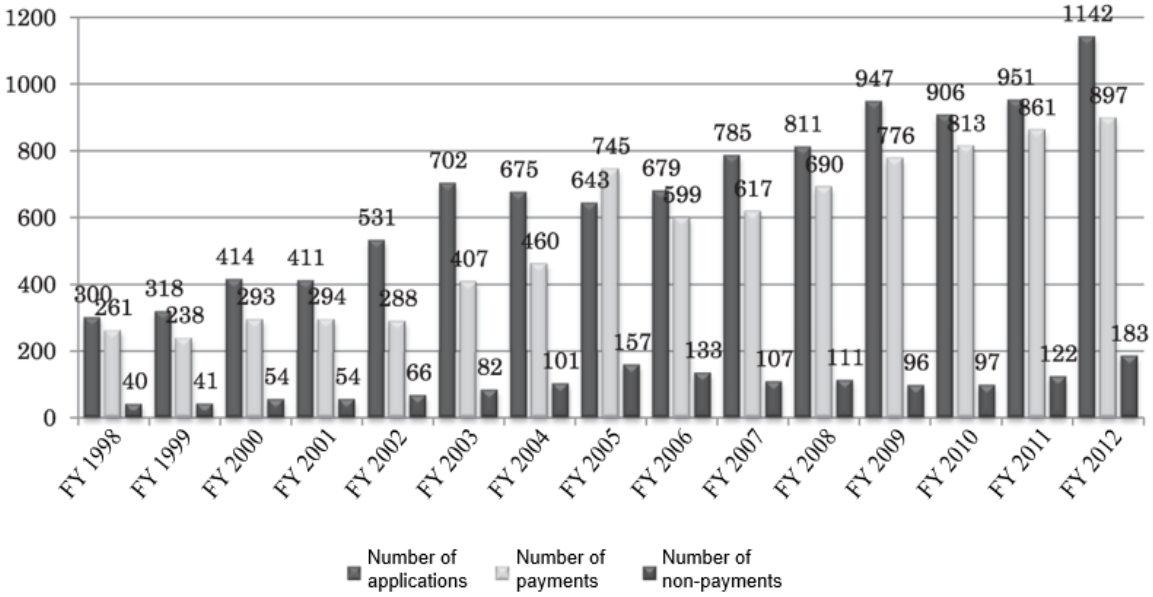
1. Introduction

The Relief System for Sufferers from Adverse Drug Reactions (Relief System) was established in 1980 to bring prompt relief to people who suffer from adverse health effects such as disorders or disabilities caused by adverse reactions to drugs (including over-the-counter drugs), despite using them properly. This is a public service funded by contributions from marketing authorization holders of drugs 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) 2012, over 12000 persons were granted relief benefits. However, the Relief System is recognized by only 20.7% of Japanese people in general; 5.3% of those surveyed answered they knew the system and 15.4% answered they have heard about the system.[Note 1)] Some people may not file an application for compensation for the adverse health effects associated with adverse drug reactions 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 people who suffer from adverse health effects associated with drug. Your cooperation in preparation of medical certificates to help patients filing an application would be appreciated.

Note 1) 2012 Awareness Survey on the Relief System for Sufferers from Adverse Drug Reactions
http://www.pmda.go.jp/kenkouhigai/ninchi/h24_ninchi_gaiyo.html
(only available in Japanese language)

Figure 1 Number of relief benefits from the Relief System



* Number of applications presents the actual number of patients who filed an application; a second claim for the same cause was not counted.

* Number of applications and total number of payments and non-payments made in the fiscal year are not consistent since a certain period is required from the receipt of the application to the decision of benefit payment.

For similar system for biological products, the Relief System for Sufferers from Diseases 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 virus, etc., despite using biological products properly. As of the end of FY 2012, 44 persons (the actual number) have been granted relief benefits.

2. Summary of adverse drug reaction relief benefit

Adverse health effects subject to adverse drug reaction relief benefit include disorders (requiring admission), disabilities (significantly activity limitation during daily life), and deaths despite properly using drugs occurred after May 1, 1980. Drugs referred to in the Relief System include all drugs approved by the Minister of Health, Labour and Welfare. While drugs given at hospitals and clinics and those purchased at pharmacies are all subject to the relief benefit, some drugs such as anticancer drugs and immunosuppressants are not.

A summary of adverse drug reaction relief benefit made by the Relief System is shown below (as of October 1, 2013). For details of the system, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai/help/information.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 disease caused by adverse drug reactions, etc.

Medical Allowance (33,300 to 35,300 yen per month)

- Benefits are provided for costs other than medical costs for treatment of disorders caused by adverse drug reactions.

Disability Pension (Grade 1: 2,680,800 yen per year; Grade 2: 2,144,400 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 disabilities caused by adverse drug reactions, etc.

Pension for Raising Children with disabilities (Grade 1: 838,800 yen per year; Grade 2: 670,800 yen per year)

- Benefits are provided for people who are responsible for raising children under 18 who suffer from a certain degree of disabilities caused by adverse drug reactions, etc.

Bereaved Family Pension (2,344,800 yen per year for 10 years)

- Benefits are provided for bereaved families to rebuild their lives following the deaths of their main providers from adverse drug reactions, etc.

Lump-sum Allowances for Bereaved Family (7,034,400 yen)

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

Funeral Expenses (201,000 yen)

- Benefits are provided for the costs of holding funeral for the person who died from adverse drug reactions, etc.

[Cases of relief benefit payments]

<Case 1>

After orally taking NEW BESSACE EV to relieve common cold symptoms, the patient had toxic epidermal necrosis and admitted to hospital for treatment for 15 days. Medical expenses and Medical Allowance were paid.

<Case 2>

After using OMNIPAQUE 300 INJECTION SYRINGE, 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 RHEUMATREX CAPSULES, the patient had interstitial pneumonia and admitted to hospital for treatment for about 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 Biological Products, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai/kansen.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 Adverse Drug Reactions
  http://www.pmda.go.jp/kenkouhigai/file/higaikyusai.pdf
- Leaflet on the Relief System
  Relief System for Sufferers from Adverse Drug Reactions
  http://www.pmda.go.jp/kenkouhigai/ldp/file/fukusayo_leaflet.pdf
  Relief System for Sufferers from Disease Infected Biological Products
  http://www.pmda.go.jp/kenkouhigai/ldp/file/seibutuyurai.pdf
- Poster for Relief System for Sufferers from Adverse Drug Reactions
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_keiji.pdf
- Materials for medication bag
  http://www.pmda.go.jp/kenkouhigai/file/kouhou_kusuri.pdf

If adverse health effects including disorders leading to hospital admission or disabilities that result in significant limitations during his/her daily life performance that are considered to be associated with drugs, healthcare professionals should provide information regarding the Relief Systems to patients or their family and help them file a benefit claim.

Consultation service is available (including the Relief System for Sufferers from Disease Infected 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 in **Table 1**.

Table 1 Examples of cases not applicable for 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 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 product liability of the marketing authorization holders of the drug or biological product.

c. Cases where it is necessary to use the drug or biological product 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 drugs or biological products are used for a proper purpose and with a proper method.
   (e.g., cases where the drugs or biological products have been used in ways other than indications approved by the Minister of Health, Labour and Welfare, or cases where the drugs or biological products have not been used in accordance with the Precautions section in the package inserts)

e. Cases of adverse health effects caused by drugs inapplicable for the relief benefits.
   Drugs inapplicable for the relief benefits:
   (1) Drugs used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
   (2) Drugs that do not have the possibility to cause adverse reactions, including drugs not used directly on human bodies or drugs without pharmacological effects (insecticides, disinfectant agents, and 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 drugs 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)"

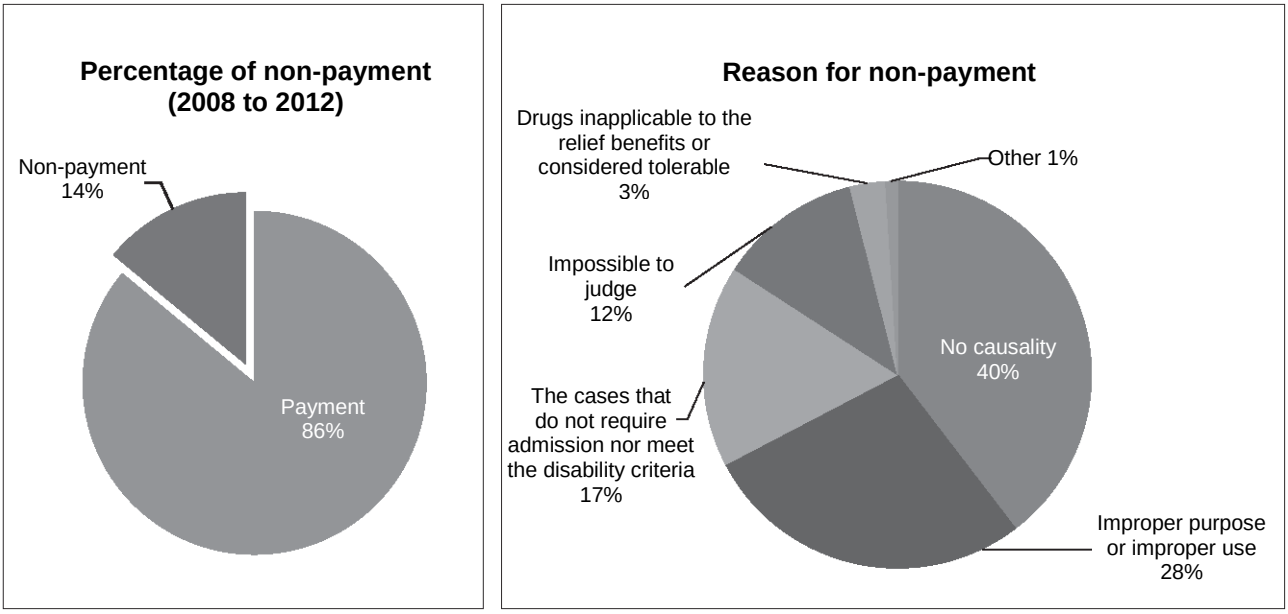
g. Cases where the deadline of claiming the relief benefits has passed.

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 adverse drug reactions (those that are not considered to be associated with drugs).
   - Cases where it cannot be judged whether there are causalities or whether drugs are used for the proper purpose and with the proper method, because of insufficient documentation (impossible to judge).

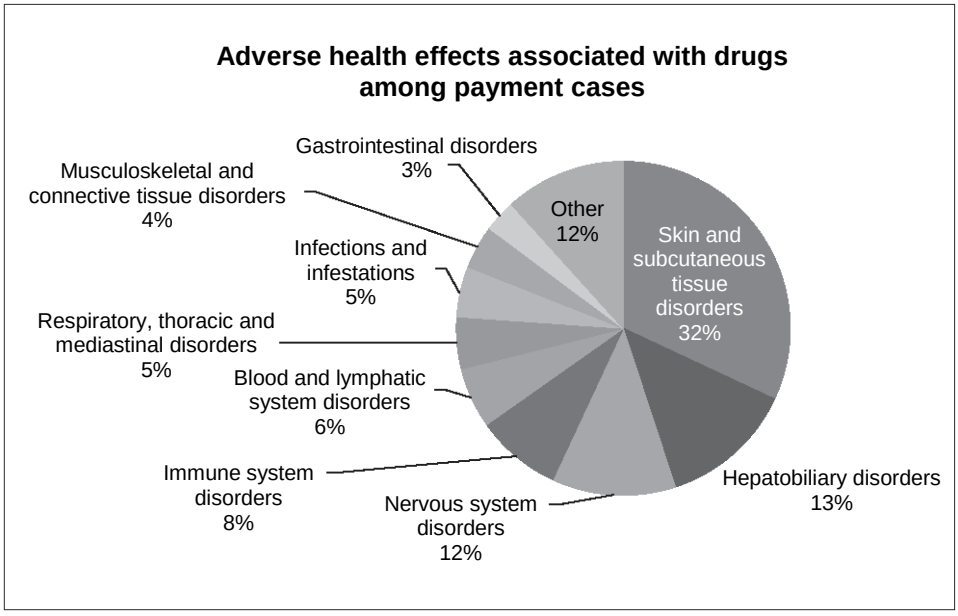
4. Summary of payment/non-payment cases in the Relief System

Between FY 2008 and FY 2012, the percentage of payments and non-payments was 86% and 14%, respectively. Details of adverse health effects associated with drugs among cases receiving payments and reasons for non-payments are shown in **Figure 2**.

Figure 2 Percentage for payments and non-payments with details of adverse health effects and reasons for non-payments between FY 2008 and FY 2012



Reason for non-payment for a total 743 cases which were determined to not receive payments among all 5249 claims between FY 2008 and FY 2012



A total of 6118 adverse health effects associated with drug are summarized by MedDRA/J System Organ Class based on 4496 cases which were determined to receive payments between FY 2008 and FY 2012.

5. Cases where it is not confirmed that the drugs are used for the proper purpose and with the proper method

Of 743 non-payment cases between FY 2008 and FY 2012,[Note 2)] 28% of these cases were determined to not receive payments because it is not confirmed that the drugs are used for the proper purpose and with the proper method. The reasons for non-payment are presented together with the description in package inserts or specific cases.

Note 2) Number of claimants: a second claim for the same cause was counted.

(1) Cases where patients take the drug by self-judgment rather than the instruction of physicians

Cases where an ethical drug prescribed by a physician was used based on the patient's self-judgment without instruction of physicians or where an ethical drug prescribed to a family member or a friend was used were considered to be the cases where it is not confirmed that the drugs are used for the proper purpose and with the proper method. Healthcare professionals are encouraged to specifically advise patients about the optimal timing and dosage to help patients properly use drugs.

<Case 1> Use of an antibiotic prescribed for cold symptoms by self-judgment

The patient took an antibiotic cefaclor prescribed half a year ago for common cold symptoms and subsequently had erythema multiforme-type drug eruption. In this case, the drug prescribed for the treatment of pharyngitis in the past was used by self-judgment.

<Case 2> Use of a drug prescribed to a friend

The patient took an over-the-counter antipyretic analgesics together with Mucosta tablets prescribed to a friend for cold symptoms and subsequently had an anaphylactoid reaction. In this case, the patient used the drug prescribed to another person by self-judgment.

(2) Cases where necessary tests are not performed

Some cases where necessary tests specified in the package insert had not been performed were considered to be the cases where it is not confirmed that the drugs are used with the proper method. Specific tests should be performed to ensure early detection of adverse drug reactions and avoid symptom aggravation. Healthcare professionals should pay attention to the Precautions section of the package insert to ensure proper use of drug.

<Drugs with many cases where necessary tests are not performed and related adverse drug reactions>

- Agranulocytosis associated with thiamazole (MERCAZOLE)
  The Warnings section specifies that, blood tests including differential leukocyte count should be performed once every 2 weeks in principle for at least 2 months after administration and periodically after that.
- Agranulocytosis and drug-induced liver injury associated with ticlopidine hydrochloride (ex. Panaldine)
  The Warnings section specifies that, blood count (including differential leukocyte count) and liver function tests should be performed once every 2 weeks in principle for at least 2 months after administration.
- Fulminant hepatitis associated with benzbromarone (ex. URINORM)
  The Warnings section specifies that, liver function tests should be periodically performed for at least the first 6 months after administration and patients should be carefully monitored.
- Agranulocytosis associated with salazosulfapyridine (ex. Azulfidine)
  The Important Precautions section specifies that, periodic haematological and liver function tests should be performed (once every 2 weeks in the first 3 months, once every 4 weeks in the next 3 months, and once every 3 months after 6 months of administration).
- Lithium poisoning associated with lithium carbonate (ex. LIMAS)

The Precautions of Dosage and Administration section specifies the following description; The serum lithium level should be measured about once weekly at the initial phase of administration and during dose-increase phase until the maintenance dose is fixed, and about once every 2 to 3 months during the maintenance dose phase. Lithium carbonate should be used while assessing a trough level based on the results of lithium level measurement. If the patient has any factor that may increase the serum lithium level (e.g., lack of food and water intake, susceptibility to dehydration, concomitant use of drugs that may increase the serum lithium level such as nonsteroidal anti-inflammatory drugs), or any initial symptom of lithium poisoning, serum lithium level should be measured.

(3) Cases where the drugs were used in ways other than approved indications, dosage and administration

Cases where the drugs were used in ways other than approved indications or dosage and administration was also considered to be the case where it is not confirmed that the drugs are used for the proper purpose and with the proper method.

<Case 1 (The drugs were used in ways other than approved indication)>

Drug-induced hypersensitivity syndrome associated with Lectisol

Lectisol was used for the treatment of prurigo nodularis, which is not included in the indications, resulting in drug-induced hypersensitivity syndrome. The case was considered as improper drug use since use of Lectisol for the treatment of prurigo nodularis is supported by no evidence.

<Case 2 (The drugs were used in ways other than approved dosage and administration)>

Severe drug eruption associated with lamotrigine (ex. Lamictal Tablets)

i) Lamotrigine monotherapy was started at a dose of 50 mg/day when it should have been 25 mg/day to prevent recurrence/relapse of mood episodes in bipolar disorder, resulting in severe drug eruption. The case was considered as improper drug use because of the excessive initial dose of lamotrigine.

ii) Lamotrigine monotherapy was started for the treatment of bipolar disorder. Lamotrigine was used at 25 mg/day for the first 5 days, at increased dose of 50 mg/day for 2 weeks, at further increased dose of 100 mg/day for 3 days and then 200 mg/day. Severe drug eruption eventually occurred. The case was considered to be improper drug use since the dose increase intervals were too short.

Relief benefit was denied in many cases of improper use of lamotrigine resulting in severe drug eruption. Most of the cases involved incompliance with the suggested initial dosage and dose increase intervals. Dosage and administration of lamotrigine are spelled out for specific indications and concomitant drugs. 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.

(4) Cases where the drugs 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 drug by thoroughly reviewing the patient's underlying disorders, complications, allergies, past adverse reactions and medications used at other hospitals to ensure proper use of drug.

<Case 1> Use of LANSAP in a patient with a penicillin allergy

LANSAP was prescribed for a patient with a history of drug eruption associated with penicillin antibiotics, resulting in erythroderma-type drug eruption.

[Contraindication]

Patients with a history of hypersensitive to ingredient of Takepron, AMOLIN, and Clarith

Note) AMOLIN contains amoxicillin hydrate, a penicillin antibiotic.

<Case 2> Use of Loxoprofen Sodium Fine Granule in a patient with a history of aspirin asthma

Loxoprofen Sodium Fine Granule was used in a patient with a history of aspirin asthma, resulting in anaphylactoid shock.

[Contraindication]

Patients with past or present aspirin asthma (asthma attack induced by non-steroidal anti-inflammatory drugs)

(5) Other cases where the drugs were used in incompliance with the package insert descriptions

<Case 1 (The drug was used incompliance with the Important Precautions section)>

Ischemic colitis associated with Laxoberon Solution

The physician did not check for usual bowel movements on the day of treatment or the day before prior to the use of Laxoberon Solution for pre-treatment for colorectal examination. The patient had had no bowel movements on the day of treatment or the day before and subsequently had ischemic colitis.

The Important Precautions section describes, ischemic colitis may occur due to an increase of bowel peristalsis and intraintestinal pressure when Laxoberon Solution is used for the pre-treatment for colorectal examination. Patients with intestinal stenosis may occur intestinal obstruction, resulting in intestinal perforation. Caution should be exercised for the following points: 1) Patient's daily bowel movements should be monitored. It should be checked that the patient has had usual bowel movements on the day or the day before using Laxoberon Solution.

<Case 2 (The drug was used incompliance with the clinically significant adverse reactions section)>

Generalized drug eruption associated with Tegretol

The patient had drug eruption associated with Tegretol Tablet and visited the dermatology department 6 days after the onset, but the treatment was continued for 8 days after that.

The clinically significant adverse reactions section specifies the following description; Serious skin symptoms may occur. Patients should be carefully monitored, if any abnormalities such as pyrexia, ocular hyperaemia, face swelling, erosion of lips/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 Precautions section of the package insert before using drugs and to use them properly. Please note that the cases where drugs are not used properly are not applicable for the relief benefits under public relief systems, even though the adverse health effects are suspected to have been caused by adverse drug reactions.

When adverse drug 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, if the reactions are possibly applicable for the relief benefits. MHLW/PMDA hopes for your particular cooperation in preparing the documents required to claim these relief benefits.

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 22, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Axitinib

Brand Name (name of company)	Inlyta Tablets 1 mg, 5 mg (Pfizer Japan Inc.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Radically unresectable or metastatic renal cell carcinoma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Cardiac failure: Cardiac failure may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 10 months (from initial marketing to June 2013)

- Cardiac failure-associated cases: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 1,800 (August 2012 to August 2013)

Launched in Japan in: August 2012

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Metastatic renal cell carcinoma (metastases to lung, metastases to central nervous system, hypercalcaemia)	10 mg for 14 days	**Acute cardiac failure** Prior treatment for renal cell carcinoma: Interferon alfa (IFNα), temsirolimus, and sunitinib malate. History of surgery or radiotherapy for renal cell carcinoma: Nephrectomy and radiotherapy Sites of metastasis: Brain and lungs Day 1 of administration: The patient was admitted to hospital for the treatment with axitinib. At hospital admission, exertional dyspnoea and impaired appetite occurred. Administration of axitinib was started at 5 mg twice daily. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 2 to 3. Echocardiography showed no wall motion abnormality. Chest X-ray showed no increase in left pleural effusion. Day 8 of administration: Systolic blood pressure was at the 140 mmHg level.

				Day 10 of administration: Systolic blood pressure was at the 150 mmHg level and seemed to tend to increase. Day 12 of administration: Systolic blood pressure decreased to the 120 mmHg level. Day 14 of administration (day of discontinuation): Malaise in extremities occurred. Calcium level (Ca) was measured and the level was 8.2 mg/dL (9.2 mg/dL after correction) within the normal range. C-reactive protein (CRP) decreased to the 2 mg/dL level. Hemoglobin (Hb) increased to 8.7 g/dL and anaemia slightly improved. From the evening, queasy appeared, thereby making it impossible to take a meal. Palpitations were observed. Heart rate was 105 bpm. Administration of axitinib was discontinued. 1 day after discontinuation: Dyspnoea occurred from the morning. Cold sweat and oedema were found. Systolic blood pressure was at the 140 mmHg level. Oxygen saturation (SpO2) decreased to between 93% to 94%. Chest X-ray showed images of cardiomegaly and pulmonary congestion, and consequently the patient was diagnosed with acute cardiac failure. Echocardiography showed diffuse myocardial disorder and left ventricular ejection fraction (LVEF) of 29%. Administration of diuretic and dobutamine was started. Coronary artery disease was ruled out by coronary angiography (CAG). 2 days after discontinuation: Creatine kinase (CK) was 245 U/L, the highest level, and then started to decrease. 6 days after discontinuation: The patient recovered from acute cardiac failure. Wall-motion improved. Chest X-ray showed improvement of pulmonary congestion. Administration of dobutamine was discontinued.
	Concomitant medication: loxoprofen sodium hydrate			

Laboratory Examination

	Day 1 of administration	Day 14 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation
Systolic blood pressure (mmHg)	101	132	140-150	-
Diastolic blood pressure (mmHg)	61	93	-	-
Hb (g/dL)	8.0	8.7	-	-
WBC (cells/mm^3)	3,600	-	-	-
Eos (%)	0.8	-	-	-
Neu (%)	67.4	-	-	-
Baso (%)	0.3	-	-	-
Lym (%)	22.5	-	-	-
Mono (%)	9.0	-	-	-
CK (U/L)	14	-	-	245
K (mEq/L)	5.1	-	-	-
Ca (mg/dL)	9.0	8.2	-	-
CRP (mg/dL)	14.45	2-3	-	-
SpO_2 (%)	96-97	97	93-94	-
LVEF (%)	85	-	29	-

2 **Bevacizumab** (Genetical Recombination)

Brand Name (name of company)	AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Incurable, unresectable, advanced/recurrent colorectal cancer; unresectable, advanced/recurrent non-small cell lung cancer except for squamous cell carcinoma; inoperable or recurrent breast cancer; malignant glioma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Thrombotic microangiopathy: Thrombotic microangiopathy such as thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome may occur. Patients should be carefully monitored through periodic tests, and if anaemia with schizocyte, decreased platelets, renal impairment, and other signs and symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 4 months (April 2010 to June 2013)

- Thrombotic microangiopathy-associated cases: 6 cases (2 fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 43,000 (February 2012 to February 2013)
Launched in Japan: June 2007

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Rectal cancer (hypertension)	mFOLFOX 6 therapy + bevacizumab, dosage unknown for approx. 5 months ↓ FOLFIRI therapy + bevacizumab 5 mg/kg once every 3 weeks, 5 courses	**Thrombotic thrombocytopenic purpura** Body height, approximately 160 cm; body weight, unknown The patient was diagnosed with new-onset rectal cancer 4 months before administration of bevacizumab. Histological type was adenocarcinoma, tumour-metastasis-node (TMN) classification at diagnosis was Stage IV M1, and site of primary lesion was upper rectum. 125 days before administration: The patient started receiving 5-fluorouracil/leucovorin plus oxaliplatin (mFOLFOX6) therapy (for approx. 4 months). Day 1 of administration: mFOLFOX6 therapy + bevacizumab was started (for approx. 5 months). PS at the start of administration was 0, primary lesion was noted, Metastases to lung and liver were found. 152 days after administration: A first course of 5-fluorouracil/leucovorin plus irinotecan (FOLFIRI) therapy + bevacizumab was performed. 166 days after administration: The patient noticed palpitations and shortness of breath at the outpatient visit. 168 days after administration: Diarrhoea occurred from around this time. No pyrexia occurred and laboratory tests did not show inflammation. 175 days after administration: A second course was performed.

				193 days after administration: Pyrexia appeared from around this time, but started to be reduced quickly. 196 days after administration: A third course was performed. 217 days after administration: A 4th course was performed. Stomatitis appeared after completion of the 4th course. 238 days after administration (day of last administration): A 5th course was performed without bolus 5-fluorouracil (5-FU). Stomatitis was mild, but diarrhoea appeared. 14 days after completion: The patient visited an outpatient department. 17 days after completion: A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity was 17.1%. 18 days after completion: Diarrhoea appeared. 19 days after completion: As pyrexia and chills (of unknown degree of seriousness) appeared, the patient was admitted to hospital. Bacteriological examination on diarrhoea was not performed. Computed tomography (CT) showed no obvious focus of pyrexia. Pyrexia persisted. 21 days after completion (day of onset): Blood test showed exacerbation of inflammation and decreased platelets. Intravenous hyperalimentation (IVH) port was removed. Administration of antibiotic was started. Disturbed orientation and depressed level of consciousness were observed in the evening. Melaena, epistaxis, and bloody sputum appeared. Renal function aggravated. Urine output decreased. The physician of the patient consulted with the hematology department and the patient was diagnosed with thrombotic thrombocytopenic purpura (TTP). Plasma exchange was started. After the first exchange, level of consciousness, general malaise, bloody sputum, etc. improved temporarily. 22 days after completion: The level of consciousness was depressed again in the early morning. Melaena and bloody sputum were exacerbated. Death was confirmed in the morning. Cause of death was TTP, autopsy was not performed.
	Concomitant medications: oxaliplatin, irinotecan hydrochloride hydrate, fluorouracil, levofolinate calcium, famotidine, pyridoxal phosphate hydrate, amlodipine besilate, dexamethasone sodium phosphate, granisetron hydrochloride			

Laboratory Examination

	151 days after administration	174 days after administration	195 days after administration	216 days after administration	237 days after administration	14 days after completion	19 days after completion	21 days after completion (1st)	21 days after completion (2nd)	22 days after completion
RBC ($\times 10^4/mm^3$)	305	287	264	277	303	291	259	234	241	243
Hb (g/dL)	9.1	8.9	8.0	8.4	9.1	8.6	7.8	7.6	7.4	7.3

Ht (%)	30.2	29.2	26.2	28.0	29.8	28.5	25.3	24.6	23.2	23.3
Plt ($\times 10^4/mm^3$)	25.6	24.5	21.1	27.7	32.3	23.1	22.8	4.9	2.7	1.7
CRP (mg/dL)	1.2	1.1	2.0	1.1	1.9	0.5	2.4	15.7	19.4	13.0
T- Bil (mg/dL)	0.53	0.60	0.39	0.35	0.35	0.34	0.47	2.28	2.26	4.00
AST (GOT) (IU)	73	80	51	79	61	58	75	255	688	528
ALT (GPT) (IU)	12	16	9	11	8	11	13	31	75	58
LDH (IU)	361	303	287	287	310	240	339	1,091	2,299	2,383
Serum Cr (mg/dL)	0.8	0.9	0.8	0.8	0.8	0.8	1.1	2.5	3.4	3.4
BUN (mg/dL)	11	11	11	11	13	9	14	25	33	38
e-GFR ($mL/min/1.73\ m^2$)	73.5	64.6	73.5	73.5	73.5	73.5	51.9	21.1	15.1	15.1

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Rectal cancer (early-stage gastric cancer)	5 mg/kg once every 3 weeks, 2 courses	**Thrombotic thrombocytopenic purpura** Body height, approximately 160 cm; body weight, approximately 50 kg (Approximately 1 year and 3 months before administration of bevacizumab) The patient experienced rectal cancer. Primary lesion was noted at the time of administration of bevacizumab. Peritoneal metastasis (already metastasized at the initial diagnosis of the primary lesion) and bone metastases were noted. PS was 0. Unknown date: The patient underwent surgery at another hospital. Approximately 16 months before administration: Stoma formation was performed. Approximately 15 months before administration: Radiation was performed (for 2 months). Approximately 13 months before administration: mFOLFOX6 therapy was performed (for 7 months). Approximately 5 months before administration: 5-fluorouracil/leucovorin (sLV5FU) therapy was performed (for 2 months). Day 1 of administration: A first course of bevacizumab + FOLFIRI was performed. General malaise and diarrhoea were found during hospital discharge. 21 days after administration (day of last administration): A second course was performed. Increased blood pressure and sweaty occurred temporarily at the time of administration of bevacizumab. Bevacizumab + FOLFIRI therapy was discontinued. 13 days after completion: Impaired appetite occurred and general malaise was aggravated. 15 days after completion: Fluid replacement was performed in outpatient settings. 20 days after completion: The patient was admitted to hospital. General malaise, neck

				pain, and low back pain appeared. 24-27 days after completion: Pyrexia (38°C) was observed. Pyrexia was resolved by loxoprofen sodium hydrate. 27 days after completion: Petechiae appeared at the site of stoma. 29 days after completion: Epistaxis occurred (Time unknown). Haematuria appeared. General malaise worsened at night. Unrest and depressed level of consciousness were observed. 30 days after completion (day of onset): Pyrexia of 39°C occurred. The patient was diagnosed with thrombotic thrombocytopenic purpura (TTP). Prednisolone was administered as follows: 500 mg (for 3 days) → 50 mg (until 53 days after completion) → 40 mg (from 54 days after completion). 31 days after completion: Level of consciousness improved. Plasma exchange was started (performed 31, 32, 34, 36, 39, and 43 days after completion). Packed red blood cell was administered at 31, 32, 33, 47, 53, and 54 days after completion of administration. When plasma exchange was discontinued, haematuria appeared, platelets decreased, T-Bil increased, and other events occurred, thereby making withdrawal difficult. 33 days after completion: ADAMTS13 activity was 43.3% 44 days after completion: The regimen was shifted to palliative treatment. Haematuria and general malaise appeared. 49 days after completion: A small amount of bloody sputum appeared. 50 days after completion: Level of consciousness became depressed gradually. Dyspnoea occurred. Administration of oxygen was started. 58 days after completion: Death was confirmed in the morning. Cause of death was TTP, autopsy was not performed.
	Concomitant medications: irinotecan hydrochloride hydrate, fluorouracil, levofolinate calcium, Rabeprazole sodium, pyridoxal phosphate hydrate, brotizolam, antibiotic-resistant lactic acid bacteria preparation, loxoprofen sodium hydrate, granisetron hydrochloride, dexamethasone sodium phosphate			

Laboratory Examination

	20 days after administration	20 days after completion	30 days after completion	33 days after completion	36 days after completion	41 days after completion	47 days after completion	50 days after completion	53 days after completion	58 days after completion
RBC ($\times 10^4/mm^3$)	345	297	218	205	267	253	178	191	130	197
Hb (g/dL)	11.1	9.5	6.9	6.2	8.1	8.0	5.9	6.3	4.3	6.4
Ht (%)	33.8	29.0	20.3	18.1	24.7	24.6	18.2	19.5	14.0	20.7
Plt ($\times 10^4/mm^3$)	19.3	16.7	4.8	2.5	4.7	6.5	3.0	2.1	3.4	1.0
CRP (mg/dL)	0.9	2.8	10.1	2.5	0.6	0.9	3.4	3.7	5.2	19.8
T- Bil (mg/dL)	1.13	0.67	4.20	1.75	1.72	2.03	1.65	2.15	1.81	6.41
AST (GOT) (IU)	49	27	358	35	46	-	39	51	94	237
ALT (GPT) (IU)	14	11	43	16	47	-	-	38	74	89

LDH (IU)	360	295	3,980	775	678	638	732	819	1,177	2,386
Serum Cr (mg/dL)	0.8	0.8	1.4	1.3	0.9	0.7	0.6	0.7	1.4	2.0
BUN (mg/dL)	7	9	26	49	28	19	25	26	92	62
e-GFR (mL/min/1.73 m^2)	72.0	72.0	39.0	42.3	63.3	83.3	98.6	83.3	39.0	26.4

3

Revision of Precautions (No. 251)

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 Notification dated October 22, 2013 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Antiepileptics

Clobazam

Brand Name

MYSTAN Tablet 5 mg, 10 mg, MYSTAN Fine Granule 1%
(Dainippon Sumitomo Pharma Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome): Patients should be carefully monitored, and if any abnormalities such as pyrexia, erythema, blister/erosion, pruritus, ocular hyperaemia, and stomatitis are observed, administration of this drug should be discontinued, and appropriate measures such as administration of corticosteroid should be taken.

2 Antihypertensives

Olmesartan Medoxomil
Olmesartan Medoxomil/Azelnidipine

Brand Name

OLMETEC TABLETS 5 mg, 10 mg, 20 mg, 40 mg
(Daiichi Sankyo Company, Limited)
REZALTAS COMBINATION TABLETS LD, HD
(Daiichi Sankyo Company, Limited)

Adverse Reactions (clinically significant adverse reactions)

Severe diarrhoea: Severe diarrhoea associated with decreased weight may occur with long-term administration. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. Intestinal villi atrophy, etc. based on biopsy has been reported.

3 Hyperlipidaemia agents

Omega-3 Fatty Acid Ethyl Ester

Brand Name

LOTRIGA Granular Capsule 2 g (Takeda Pharmaceutical Company Limited)

Adverse Reactions (clinically significant adverse reactions)

Hepatic dysfunction, jaundice: Hepatic dysfunction and/or jaundice with elevations of AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH, bilirubin, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

4 **Anticoagulants**

Apixaban

Brand Name	Eliquis tablets 2.5 mg, 5 mg (Bristol-Myers K.K.)
Important Precautions	In patients undergoing elective surgery or invasive surgery, administration of this drug should be temporarily discontinued according to the risk of haemorrhage and thrombus. If a surgery or invasive procedure is performed with a low risk of, or limited and controllable haemorrhage, it is desirable to have an administration interval of at least 24 hours. Also, if a surgery or invasive procedure is performed with a medium or high risk of, or potential risk of clinically significant haemorrhage, the administration interval should be at least 48 hours. In addition, an alternative therapy (e.g. heparin) should be considered as necessary. In patients undergoing an urgent surgery or invasive procedure, the urgency and increased risk of haemorrhage should be carefully balanced and considered.

5 **Blood and body fluid agents-Miscellaneous**

Ethyl Icosapentate

Brand Name	EPADEL S300, S600, S900, EPADEL CAPSULES 300 (Mochida Pharmaceutical Co., Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction and/or jaundice with elevations of AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH, bilirubin, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.
Other Adverse Reactions	**Liver**: Hepatic dysfunction associated with events such AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH, bilirubin, etc.

6 **Antimetabolites**

Gemcitabine Hydrochloride

Brand Name	Gemzar Injection 200 mg, 1 g (Eli Lilly Japan K.K.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Leukoencephalopathy (including posterior reversible encephalopathy syndrome)**: Leukoencephalopathy (including posterior reversible encephalopathy syndrome) may occur. If signs and symptoms including hypertension, convulsion, headache, abnormal vision, and disturbed consciousness are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

7 **Antineoplastics-Miscellaneous**

Oxaliplatin

Brand Name	ELPLAT I. V. INFUSION SOLUTION 50 mg, 100 mg, 200 mg (Yakult Honsha Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Deafness**: Deafness, tinnitus, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

8

Antineoplastics-Miscellaneous

Cisplatin (non-intra-arterial injection)

Brand Name

BRIPLATIN INJECTION 10 mg, 25 mg, 50 mg (Bristol Myers K.K.), Randa Inj. 10 mg/20 mL, 25 mg/50 mL, 50 mg/100 mL (Nippon Kayaku Co., Ltd.) and the others

Adverse Reactions (clinically significant adverse reactions)

Venous thromboembolism: Venous thromboembolism such as pulmonary embolism and deep vein thrombosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

9

Antineoplastics-Miscellaneous

Regorafenib Hydrate

Brand Name

Stivarga tablets 40 mg (Bayer Yakuhin, Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Decreased platelets: Decreased platelets may occur. Patients should be carefully monitored through periodic blood testing, etc. during treatment with this drug. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or discontinuation of administration should be taken.

10

Cardiovascular agents, blood agents-Miscellaneous

Over-the-counter Drug Ethyl Icosapentate

Brand Name

Epadel T, EPA-ARTE (Mochida Pharmaceutical Co., Ltd.)

Consultation

The following symptoms may be adverse reactions, therefore if the following symptoms are observed, immediately discontinue this drug, and contact a physician or a pharmacist for a consultation with this package insert.

The following serious symptoms occur infrequently. Immediately seek medical aid if you experience any of these signs and symptoms.

Hepatic dysfunction: Pyrexia, itching, rash, jaundice (skin and whites of the eyes become yellow), brown urine, general malaise, inappetence, etc. may occur.

4

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 new drugs. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for 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 adverse drug reactions. EPPV is specified as a condition of approval.

(As of November 1, 2013)

◎: Newly-posted products, or products changed from the last Bulletin

	Nonproprietary name / Brand name	Name of the marketing authorization holder	Date of EPPV initiate
◎	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) Prevenar13 Suspension Liquid for Injection	Pfizer Japan Inc.	October 28, 2013
◎	Hydroxyethylated Starch 130000 VOLUVEN 6% solution for infusion	Fresenius Kabi Japan K.K.	October 25, 2013
	Fentanyl Citrate E-fen buccal tablet 50 μg, 100 μg, 200 μg, 400 μg, 600 μg, 800 μg	Teikoku Seiyaku Co., Ltd.	September 26, 2013
	Norethisterone/Ethinylestradiol LUNABELL tablets ULD	Nobelpharma Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride ALAGLIO Oral 1.5 g	SBI Pharmaceuticals Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride Alabel Oral 1.5 g	Nobelpharma Co., Ltd.	September 18, 2013
	Lixisenatide Lyxumia Subcutaneous Injection 300 μg	Sanofi K.K.	September 17, 2013
	Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 μg PLASTIC SYRING, 15 μg PLASTIC SYRINGE, 20 μg PLASTIC SYRINGE, 30 μg PLASTIC SYRINGE, 40 μg PLASTIC SYRINGE, 60 μg PLASTIC SYRINGE, 120 μg PLASTIC SYRINGE, 180 μg PLASTIC SYRINGE*[1]	Kyowa Hakko Kirin Co., Ltd.	September 13, 2013
	Tolvaptan Samsca tablets 7.5 mg*[2]	Otsuka Pharmaceutical Co., Ltd.	September 13, 2013
	Eculizumab (Genetical Recombination) Soliris Drip Infusion 300 mg*[3]	Alexion Pharma G.K.	September 13, 2013
	Pertuzumab (Genetical Recombination) PERJETA Intravenous Infusion 420 mg/14 mL	Chugai Pharmaceutical Co., Ltd.	September 12, 2013
	Bisoprolol Bisono tape 4 mg, 8 mg	Toa Eiyo Ltd.	September 10, 2013

	Irbesartan/Trichlormethiazide Irtra Combination Tablets LD, HD	Shionogi & Co., Ltd.	September 4, 2013
	Topiroxostat (1) TOPILORIC Tablets 20 mg, 40 mg, 60 mg (2) URIADEC Tab. 20 mg, 40 mg, 60 mg	(1) Fujiyakuhin Co., Ltd. (2) Sanwa Kagaku Kenkyusho CO., LTD.	September 4, 2013
	Ibandronate Sodium Hydrate Bonviva IV Injection 1 mg Syringe	Chugai Pharmaceutical Co., Ltd.	August 29, 2013
	Levetiracetam E Keppra Dry syrup 50%	UCB Japan Co. Ltd	August 29, 2013
	Abatacept (Genetical Recombination) ORENCIA SYRINGE FOR S.C. INJECTION 125 mg/1 mL	Bristol-Myers K.K.	August 27, 2013
	Hemin Normosang Infusion 250 mg	Orphan Pacific, Inc.	August 23, 2013
	Palivizumab (Genetical Recombination) Synagis for Intramuscular Injection 50 mg, 100 mg*4 Synagis Intramuscular Solution 50 mg, 100 mg*4	AbbVie G.K.	August 20, 2013
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*5	Novartis Pharma K.K.	August 20, 2013
	Omalizumab (Genetical Recombination) Xolair for s.c. injection 150 mg, 75 mg*6	Novartis Pharma K.K.	August 20, 2013
	Tofacitinib Citrate XELJANZ Tablets 5 mg	Pfizer Japan Inc.	July 30, 2013
	Metreleptin (Genetical Recombination) Metreleptin for Subcutaneous Injection 11.25 mg "SHIONOGI"	Shionogi & Co., Ltd.	July 25, 2013
	Saxagliptin Hydrate ONGLYZA Tablets 2.5 mg, 5 mg	Kyowa Hakko Kirin Co., Ltd.	July 9, 2013
	Oxybutynin Hydrochloride NEOXY TAPE 73.5 mg	Hisamitsu Pharmaceutical Co., Inc.	June 27, 2013
	Clofarabine Evoltra 20 mg I.V. Infusion	Sanofi K.K.	June 21, 2013
	Lidocaine Penles Tape 18 mg*7	Nitto Denko Corporation	June 14, 2013
	Tacrolimus Hydrate Prograf Capsules 0.5 mg, 1 mg*8	Astellas Pharma Inc.	June 14, 2013
	Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*9	Chugai Pharmaceutical Co., Ltd.	June 14, 2013
	Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg*10	Nippon Shinyaku Co., Ltd.	June 14, 2013
	Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%*11	Otsuka Pharmaceutical Co., Ltd.	June 14, 2013
	Dexmedetomidine Hydrochloride (1) Precedex Intravenous Solution 200 μg "Hospira"*12 (2) PRECEDEX Intravenous Solution 200 μg	(1) Hospira Japan Co., Ltd. (2) Maruishi Pharmaceutical Co., Ltd.	June 14, 2013

	"Maruishi"*[12]		
	Denosumab (Genetical Recombination) PRALIA SUBCUTANEOUS INJECTION 60 mg SYRINGE	Daiichi Sankyo Company, Limited	June 11, 2013
	Acotiamide Hydrochloride Hydrate Acofide Tablets 100 mg	Zeria Pharmaceutical Co., Ltd.	June 6, 2013
	Levetiracetam E Keppra Tablets 250 mg, 500 mg*[13]	UCB Japan Co. Ltd	May 31, 2013
	Istradefylline NOURIAST Tablets 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 30, 2013
	Rufinamide Inovelon Tablets 100 mg, 200 mg	Eisai Co., Ltd.	May 29, 2013
	Acamprosate Calcium Regtect Tablets 333 mg	Nippon Shinyaku Co., Ltd.	May 27, 2013
	Ofatumumab (Genetical Recombination) Arzerra for I.V. infusion 100 mg, 1000 mg	GlaxoSmithKline K.K.	May 24, 2013
	Tocilizumab (Genetical Recombination) ACTEMRA 162 mg Syringe for SC Injection, ACTEMRA 162 mg Auto-Injector for SC Injection	Chugai Pharmaceutical Co., Ltd.	May 24, 2013
	Exenatide BYDUREON for Subcutaneous Injection 2 mg	Astra Zeneca K.K.	May 16, 2013
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Stribild Combination Tab.	Japan Tobacco Inc.	May 14, 2013
	Regorafenib Hydrate Stivarga tablets 40 mg*[14]	Bayer Yakuhin, Ltd.	March 25, 2013

*1 An additional administration for “pediatrics”

*2 An additional indication for “fluid retention in patients with hepatic cirrhosis which is not adequately responded to other diuretics such as loop diuretics”

*3 An additional indication for “inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome”

*4 An additional indication for “prevention of serious lower respiratory tract disease caused by respiratory syncytial (RS) virus infection in neonates and infants aged ≤24 months with immunodeficiency or Down syndrome (early stage of an epidemic of RS viral infection)"

*5 An additional indication for “treatment of patients with macular oedema with retinal vein occlusion or choroidal neovascularization with pathologic myopia”

*6 An additional administration for “pediatrics”

*7 An additional indication for “relief of pain in laser irradiation treatment of the skin”

*8 An additional indication for “treatment of patients with interstitial pneumonia associated with polymyositis/dermatomyositis”

*9 An additional indication for “treatment of patients with malignant glioma”

*10 An additional indication for “analgesia of chronic pain cannot be managed by treatments with non-opioid analgesics”

*11 An additional indication for “treatment of patients with depression/depressive state (to be used only when the patient does not sufficiently respond to conventional therapy)”

*12 An additional indication for “sedation in surgery or treatment without intubation under local anesthesia”

*13 An additional administration for “pediatrics”

*14 EPPV was initiated in August 21, 2013 for an additional indication for “treatment of patients with gastrointestinal stromal tumour that has progressed after chemotherapy”