Pharmaceuticals and Medical Devices Safety Information

No. 328 December 2015

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

Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 328 December 2015

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Hypermagnesaemia caused by magnesium oxide**	*P* *C*	Precautions in the package inserts were revised in September 2008 in order to alert caution about hypermagnesaemia associated with use of magnesium oxide. As a result of consolidating and surveying reports of the aforementioned adverse reaction after this revision, it was determined that further caution was necessary when administering magnesium oxide to geriatric patients, etc. Relevant pharmaceutical companies were instructed to revise the precautions in the package inserts accordingly on October 20, 2015. Details of the safety measures will be presented in this section.	5
2	**Summary of the Relief System for Adverse Drug Reaction and Cases of Non-payment of Relief Benefits Due to Improper Use of Drugs**		The number of applications for the Relief System for Adverse Drug Reaction has increased in recent years. In order to ensure widespread understanding, a summary of the Relief System will be presented in this section. In addition, out of all the non-payment cases, those that did not receive relief benefits due to improper use of drugs will also be detailed in this section. Please be reminded that the MHLW and PMDA strictly encourages proper use of drugs.	9
3	**Project of the Japan Drug Information Institute in Pregnancy**		The MHLW established the “Japan Drug Information Institute in Pregnancy (JDIIP)” in the National Center for Child Health and Development in October 2005 to provide consultation services and perform surveys. Same as last year, the system was strengthened this year by receiving cooperation from newly joined hospitals. Details will be presented in this section. This section will also provide details of the forum held on November 3, 2015 to celebrate the 10th anniversary of the JDIIP.	18
4	**Important Safety Information**	*P* *C*	**Asunaprevir and daclatasvir hydrochloride:** Regarding the revision of the Precautions section of package inserts of drugs in accordance with the notification dated October 20, 2015, the contents of important revisions and case summaries that served as the basis for these revisions will be presented in this section.	24
5	**Revision of Precautions (No. 269)**	*P*	Galantamine hydrobromide (and 4 others)	27

6	**List of Products Subject to Early Post-marketing Phase Vigilance**		A list of products subject to Early Post-marketing Phase Vigilance as of October 31, 2015 will be presented in this section.	29

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, R: Distribution of Dear Healthcare Professional Letters of Rapid Communications, P: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reaction 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 reaction, 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
Alb	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
DIHS	Drug-induced hypersensitivity syndrome
DVT	Deep vein thrombosis
EPPV	Early post-marketing phase vigilance
Eos	Eosinophil
FY	Fiscal year
HPV	Human papillomavirus
HCV-RNA	Hepatitis C virus-Ribonucleic acid
IBD	Irritable bowel disease
JDIIP	Japan Drug Information Institute in Pregnancy
KL-6	Krebs von den Lunge-6
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Mg	Magnesium
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and medical devices safety information
T-Bil	Total bilirubin
WBC	White blood cell count

1

Hypermagnesaemia caused by magnesium oxide

Active ingredient	Magnesium oxide
Brand name (name of company)	Magmitt Tablets 200 mg, 250 mg, 330 mg, and 500 mg, Magmitt Fine Granules 83% (Kyowa Chemical Industry Co., Ltd.) and the others
Therapeutic category	Antacids
Indications	Improvement of antacid actions and symptoms in the following diseases: Gastroduodenal ulcer, gastritis (including acute/chronic gastritis and drug-induced gastritis), gastrointestinal dysfunction (including anorexia nervosa, so-called gastroptosis, and hyperchlorhydria) Constipation Prevent the formation of calcium oxalate urinary stone

1. Introduction

In September 2008, precautions in the package inserts were revised to include hypermagnesaemia due to administration of magnesium oxide since there were case reports of long-term administration of magnesium oxide without any probable reason and cases of serious outcomes as symptoms of hypermagnesaemia went unnoticed. The Pharmaceuticals and Medical Devices Agency (PMDA) has alerted healthcare providers about precautions regarding initial symptoms of hypermagnesaemia in the “Clinically significant adverse reaction” subsection of the “Adverse Reaction” section and precautions regarding periodic measurement of serum magnesium concentrations when the drug is administered long-term in the “Important Precautions” section.

As a result of consolidating and surveying recent reports after this revision, severe cases of hypermagnesaemia were still being reported, and it was determined that further caution was necessary. Relevant pharmaceutical companies were instructed to revise the precautions in the package inserts accordingly on October 20, 2015. The details of these safety measures are described hereinafter.

2. Onset conditions of hypermagnesaemia

Magnesium oxide has been widely used as a laxative and antacid since 1950, and relevant pharmaceutical companies estimate that the number of patients treated with magnesium oxide in 2013 was approximately 10 million.

From April 2012 to June 2015, a total of 29 cases associated with hypermagnesaemia due to administration of magnesium oxide were reported (including 4 fatal cases). Of these 29 cases, a causal relationship to the product could not be ruled out for 19 cases (including 1 fatal case).

The experts reviewed these cases and determined that many were associated to geriatric patients (65 years or older) and patients with constipation. There were serious outcomes among some of these even if the patient had normal renal function or the dosage administered was lower than the recommended dose. Furthermore, occurrence of hypermagnesaemia was not detected in many patients until serious outcomes such as loss of consciousness had occurred. Based on these facts, relevant pharmaceutical companies were instructed to revise the package inserts as follows: In the “Important Precautions” section

regarding hypermagnesaemia, add that usage should be kept to a minimum, that precautions such as periodic measurement of serum magnesium concentration should be exercised for geriatric patients in addition to prolonged use, and that patients should be instructed to discontinue use of the drug and seek medical attention immediately when the patient experiences any initial symptoms associated to hypermagnesaemia; In the "Careful Administration" section, add geriatrics; and, in the "Use in geriatrics" section, add precautions related to hypermagnesaemia in geriatrics.

Healthcare professionals should exercise further caution for the following:

- Use of magnesium oxide should be kept to a minimum.
- If magnesium oxide is administered for a prolonged period or for geriatrics, special precautions such as periodic measurement of serum magnesium concentration should be taken.
- If initial symptoms (such as vomiting, bradycardia, muscular weakness, and somnolence) are observed, patients should be instructed to discontinue use of magnesium oxide and seek medical attention immediately.

Number of cases by patient background (From April 2012 to June 2015)

		Number of reported cases	Number of cases for which a causality to the drug could not be ruled out
Total number		29 (4)	19 (1)
Age	Geriatrics (65 years and older)	21 (3)	14 (0)
	Under 65 years old	7 (1)	5 (1)
	Unknown	1 (0)	0 (0)
Intended use	Constipation	22 (3)	13 (1)
	Indication other than constipation	2 (1)	2 (0)
	Unknown	5 (0)	4 (0)
Presence/Absence of Renal impairment	Abnormal renal function	12 (0)	8 (0)
	Normal renal function	5 (1)	3 (0)
	Unknown	12 (3)	8 (1)
Dosage administered	More than 2 g/day	5 (0)	4 (0)
	2 g/day or less	15 (4)	11 (1)
	Unknown	9 (0)	4 (0)

Numbers noted in ( ) indicate fatal cases.

«PRECAUTIONS (underlined parts are revised)»

[Careful Administration] Geriatrics

[Important Precautions] Hypermagnesaemia may occur. In particular, in patients with constipation, it has been reported that hypermagnesaemia led to serious outcomes in some patients, even if the renal function was normal or the dosage was under the recommended dose. Therefore, caution should be exercised for the following points.

(1) Use of the drug should be kept to a minimum

(2) If this drug is administered for a prolonged period or for geriatrics, special precautions such as periodic measurement of serum magnesium concentration should be taken.

(3) If symptoms such as vomiting, bradycardia, muscular weakness, and somnolence are observed, patients should be instructed to discontinue this drug and seek medical attention immediately.

[Use in Geriatrics] In geriatrics, many cases have been reported in which hypermagnesaemia has led to serious outcomes. The dose should be reduced, and patients should be carefully monitored with periodic measurement of serum magnesium concentration, etc.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
1	Female 40s	Constipation (Schizophrenia)	1 980 mg Unknown	**Hypermagnesaemia, Sepsis** The patient, who was considered independent on the ADL scale, was admitted to the hospital for schizophrenia. Date unknown: Administration of magnesium oxide 1 980 mg was started. Day of onset: 2:00 The patient was confirmed to be sleeping in her bed. Day of onset: 3:00 The patient was found crouching in the bathroom. The patient had disturbed consciousness, and blood pressure was 143/99 mmHg, pulse was 76 bpm, and body temperature was 33.4°C, indicating low body temperature. Since body temperature did not resolve after being warmed, the patient was transported to a different hospital. After transfer: The patient had low blood pressure and disturbed consciousness. Magnesium was 18.4 mg/dL, indicating hypermagnesaemia. Even though the patient was loaded with extracellular fluid and diuretic effect was achieved, Mg remained at a high value, 12.8 mg/dL; therefore, the patient underwent emergency dialysis and was admitted to the hospital. After admittance to the hospital: Mg only decreased to 10 mg/dL after dialysis, and pulse decreased to 30-40 bpm and the patient went into shock associated with bradycardia. The patient was transfused and intubated, an intravenous line was established with a central vein catheter, and an intra-arterial line was inserted to manage blood pressure. Although pressor treatment was provided through 8L transfusion and administration of noradrenaline, the patient's blood pressure remained at 50-60 mmHg and pulse at 40-50 bpm and continued to be in shock associated with bradycardia. The patient did not respond to transcutaneous pacing and insertion of temporary external pacing was considered; however, the patient was considered ineligible as the patient had pyrexia and may be concomitantly suffering from sepsis. 1 day after onset: 6:00 State of consciousness worsened, blood pressure decreased, and the patient suffered from intestinal ischaemia as well as metabolic acidosis and melena associated with sepsis. 1 day after onset: 14:55 Cardiac arrest was confirmed and the patient was pronounced dead. Cause of death was determined to be hypermagnesaemia. No autopsy was conducted.

Laboratory examination

Parameters	Day of onset	2 hours later
Mg (mg/dL)	18.4	12.8
BUN (mg/dL)	18	17
Cr (mg/dL)	1.0	0.7

Concomitant medications: aripiprazole, levomepromazine maleate, biperiden hydrochloride, sodium valproate, haloperidol, blonanserin, lithium carbonate, famotidine, lamotrigine, zotepine, olanzapine, paliperidone, flunitrazepam, chlorpromazine hydrochloride/promethazine hydrochloride/phenobarbital, sennoside

Case Summary

No.	Patient: Sex/ Age	Patient: Primary disease (complications)	Daily dose/ Treatment duration	Adverse Reaction: Clinical course and therapeutic measures
2	Male 80s	Unknown (Schizophrenia)	1 980 mg Unknown	**Hypermagnesaemia** Day of admittance to the hospital: The patient was transported emergently after decrease in consciousness was observed while being admitted in a medical institution. Consciousness level was 300 on the Japan Coma Scale (JCS). The patient had bradycardia, lowered blood pressure, and abnormal electrocardiogram when brought to the hospital. Mg was 13.3 mg/dL. Calcium gluconate was administered. Hemodialysis was conducted. As the patient had hemodynamic instability, treatment was switched to continuous hemodiafiltration (CHDF). 2 days after admittance to the hospital: Consciousness level was resolving on the Glasgow Coma Scale to E4VTM6. 9 days after admittance to the hospital: The patient was transferred to the general ward after good general conditions were confirmed. 24 days after admittance to the hospital: The patient was discharged from the hospital and admitted again to the medical institution.

Laboratory examination

Parameters	Day of admitt-ance	1 day after admitt-ance	2 days after admitt-ance	3 days after admitt-ance	4 days after admitt-ance	7 days after admitt-ance	10 days after admitt-ance	20 days after admitt-ance
Mg (mg/dL)	13.3	7.4	4.8	2.2	2.8	3.8	2.2	2.1

Concomitant medications: olanzapine, biperiden hydrochloride, trihexyphenidyl hydrochloride, haloperidol, sodium valproate

2

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

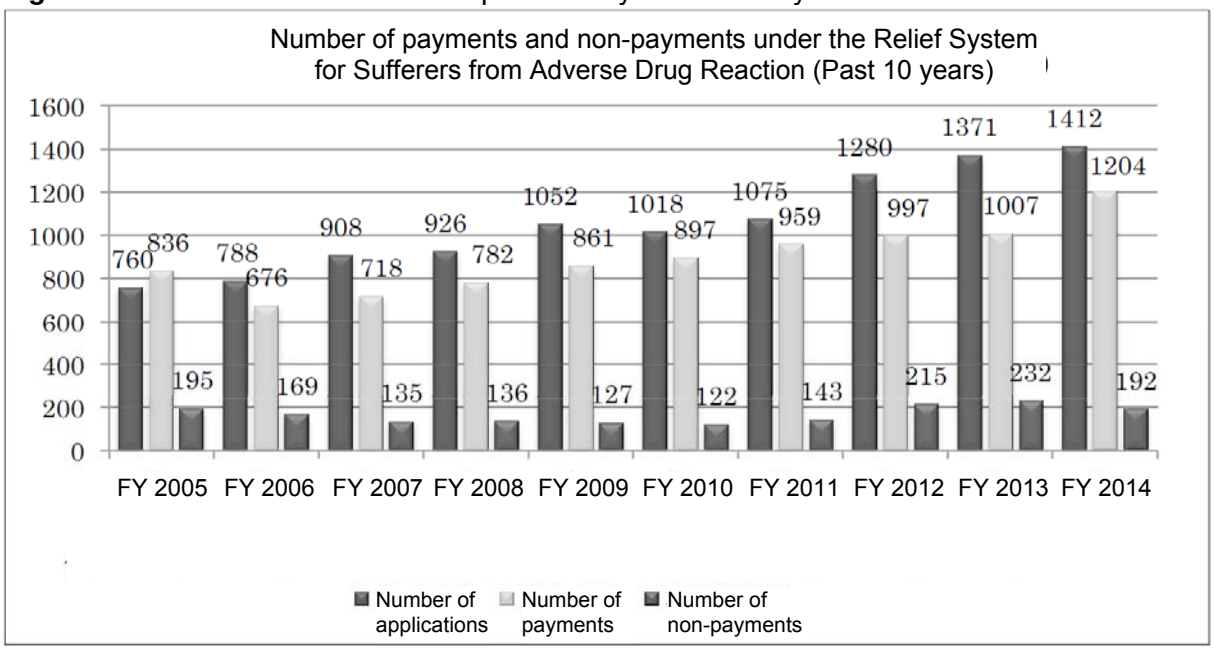
1. Introduction

The Relief System for 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 reaction 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 part 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) 2014, over 16 500 persons were granted relief benefits. However, the Relief System is recognized by only 21.8% of Japanese people in general; 5.4% of those surveyed answered they knew the system and 16.4% answered that they have heard about the system. Note 1) It is inferred that some people may not file an application for compensation for adverse health effects associated with ADR they have suffered because they are unaware of the Relief System. Healthcare professionals are encouraged to provide information on the Relief System to patients or their families if such adverse health effects occur. In addition, healthcare professionals are encouraged to provide assistance in preparing medical certificates, etc. for patients filing an application.

Note 1) 2014 Awareness Survey on the Relief System for Sufferers from ADR
(only available in Japanese language)
https://www.pmda.go.jp/relief-services/adr-sufferers/0023.html

Figure 1 Number of relief benefits provided by the Relief System



(Explanation for the figure)
*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.

A similar system for biological products, the Relief System for Infections Acquired through 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 etc., despite using biological products properly. As of the end of FY 2014, 73 persons have been granted relief benefits.

In addition, adverse reaction and infection 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, 2015). For details of the system, please refer to the PMDA website.
(https://www.pmda.go.jp/english/relief-services/0002.html)

[Cases of relief benefit payments]
<Case 1>

After taking carbamazepine (Tegretol Tablets) for treatment of epilepsy, the patient had drug-induced hypersensitivity syndrome (DIHS) and was admitted to the hospital for treatment for approximately 1 month. Medical Expenses and Medical Allowance were paid.

<Case 2>

After taking ethambutol hydrochloride (Ebtol Tablets) for treatment of non-tuberculous mycobacteriosis, the patient was left with visual impairment associated with toxic optic neuropathy. Disability Pension was paid.

<Case 3>

After taking sodium valproate (Depakene-R Tablets), the patient had fulminant hepatitis which resulted in death. Medical Expenses, Medical Allowance, Lump-sum Allowances for Bereaved Family, and Funeral Expenses were paid.

<Case 4>

After using irradiated red cells concentrates (Ir-RCC), the patient had cardiac failure due to transfusion-related circulatory overload (TACO), which resulted in death. Medical Expenses, Medical Allowance, Lump-sum Allowances for Bereaved Family, and Funeral Expenses were paid.

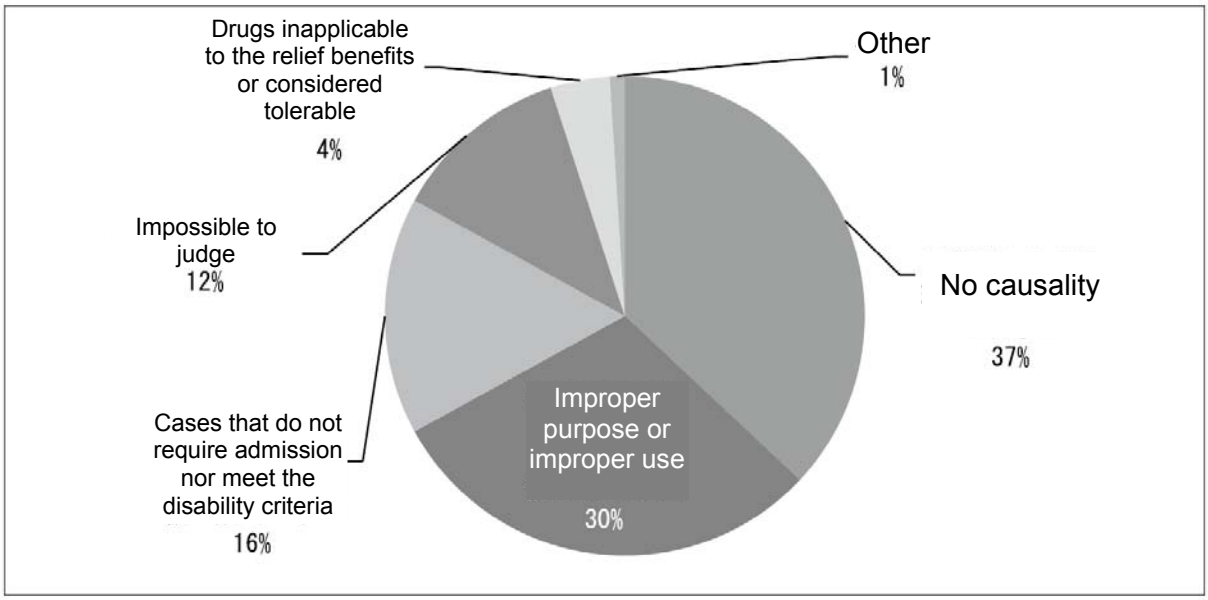
3. Summary of payment/non-payment cases in the Relief System

Between FY 2010 and FY 2014, the percentage of payments and non-payments was 85% and 15%, respectively. Details of 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 of cases for which payment or non-payment was determined. The actual achievement percentage in FY 2014 was 61.9%.

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 judgements, are excluded from the administrative processing time from claim submission to payment approval/rejection judgements.

Figure 2 Reasons for non-payments between FY 2010 and FY 2014



(Explanation for the figure)
Breakdown of the reasons for non-payment for the 904 non-payment cases of the 5 980 claims decided between FY 2010 and FY 2014

4. Information on human papillomavirus (HPV) vaccinations

As of September 30, 2015, the Relief System has granted payment to 18 cases of HPV vaccinations sufferers and rejected 9 cases.

The joint meeting of the Adverse Reaction Review Committee for Preventive/Voluntary Vaccination on the Health Sciences Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council was held on September 17, 2015, and the results of the national tracking survey were presented. According to the findings, after HPV vaccines were administered, some people suffered from various symptoms not localized to the injection site such as pain and numbness, which affected the people's lives such as being unable to go to school or work.

Based on these results, the MHLW decided that "a causal relationship to the HPV vaccination could not be ruled out" for 13 cases, in which patients claimed adverse health effects such as pain. Payment of relief benefits have been confirmed for 5 cases as of October 31, 2015; payment for the remaining 8 cases will be deliberated after receipt of additional documents.

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

As shown in **Figure 2**, in 30% of the 904 non-payment cases between FY 2010 and FY 2014 Note 3), the reason for non-payment 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

The most common reason why the use of a drug is not considered proper is the dosage and administration was not approved, and cases using lamotrigine (Lamictal Tablets) account for a large majority of those cases. Cases where the pharmaceuticals were used in ways other than the approved dosage and administration are presented here.

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

Improper use of lamotrigine

a. Administration of more than the recommended dosage and noncompliance with dose increase intervals

According to domestic clinical trials, serious drug eruption due to lamotrigine occurred in higher frequency with administration of a dose higher than the recommended dose. Healthcare professionals have been repeatedly encouraged to adhere to the recommended administration methods through various means including the distribution of the Dear Healthcare Professional Letters of Rapid Safety Communications in February 2015.

Even though constant reminders have been disseminated and a slight decrease in improper use has been seen, there are still many cases where relief benefits are not paid for serious drug eruption associated with use of lamotrigine because of improper use of the drug. In most of these non-payment cases, patients were prescribed excessive doses for the initial dosage or dose increase intervals were not adhered to. 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.

Healthcare professionals should comply with the dosage and administration as stated in the package insert of this drug.

The incidence of skin disorders was increased when this drug was administered at doses higher than recommended dosage and frequency of administration.

- During the initial phase of treatment, this drug should not be used at doses higher than the recommended dosage and frequency of administration.
- When used concomitantly with sodium valproate, this drug should be administered on alternate days for the first 2 weeks (only for adult patients).
- This drug should not be used at doses higher than recommended dosage and frequency of administration during dose titration before establishing the maintenance dose.
- A dose increase should not be attempted earlier than the specified timing.

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

- The following symptoms in addition to a rash might indicate the development of a serious skin disorder. Administration of this drug should be discontinued immediately.
  - ○ Pyrexia (38°C or above)
  - ○ Ocular hyperaemia

○ Lip/oral mucosa erosion ○ Pharyngodynia
○ General malaise ○ Lymphadenopathy, etc.

- Delay in the treatment of skin disorders might lead to a serious outcome. Healthcare professionals should consult with a dermatologist at an early stage, and appropriate measures should be taken.
- Patients and their family should be advised to see a doctor immediately and tell a doctor or pharmacist that they are being treated with this drug if a rash and/or the above symptoms occur.

From the Dear Healthcare Professionals Letter of Rapid Safety Communication in February 2015 “Serious skin disorders suggestively caused by Lamictal tablets”

b. Concomitant administration of sodium valproate and lamotrigine for bipolar disorder

The package insert of lamotrigine specifically indicates “25 mg of lamotrigine will be orally administered once every other day for the first 2 weeks and then once daily for the next 2 weeks...” In other words, Day 14 of the first 2 weeks of administration should be a rest period, and daily administration should only begin on Day 15. If an extra dose is administered on Day 14, lamotrigine will be administered daily from Day 13 instead of Day 15, and is therefore considered improper use of the drug.

<Case Report> Case of non-payment due to improper use of lamotrigine (Lamictal tablets) when concomitantly administered with sodium valproate

The patient was orally administered Lamictal tablets once every other day and Day 14 should have been a rest period. Instead, the drug was administered on Day 14 as well, which meant the patient was administered the drug daily since Day 13. As a result, the patient had DIHS.

<Example of Improper Use>

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

For this case, Day 14 should have been a rest period as indicated in the <Example of Proper Use> below. Healthcare professionals should exercise caution when prescribing or instructing patients on administration of the drug so that similar accidents can be avoided.

<Example of Proper Use>

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

Furthermore, pharmaceutical companies have created various materials regarding proper use of their products. Medical institutions are encouraged to utilize such materials, etc. within their facility to ensure proper use.

(2) Cases where the pharmaceuticals used were those inapplicable to the relief benefits

Pharmaceuticals used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare are inapplicable for the relief benefits. Although the following case for tacrolimus is inapplicable for relief benefits, "administration of the drug for treatment of rheumatoid arthritis" is now eligible to receive relief benefits since April 1, 2013. However, caution is advised since administration of the drugs prior to April 1, 2013 (i.e. before these drugs were considered applicable for relief benefits) will be considered inapplicable for the relief benefits.

Case results regarding tacrolimus

[Pharmaceuticals inapplicable for the relief benefits] Tacrolimus (Excludes topical formulations, ophthalmic preparations, and use of the drug for rheumatoid arthritis such as 0.5 mg, 1.0 mg, 1.5 mg, and 3.0 mg tablets and 0.5 mg and 1.0 mg capsules) *Relief benefits are applicable for treatment of rheumatoid arthritis only if the drug is administered after April 1, 2013.

○ Non-payment case where tacrolimus (Prograf capsules) was administered
<Case Report> Tacrolimus was administered for the treatment of chronic rheumatoid arthritis before April 1, 2013, and the patient had gastric ulcer followed by pyloric stenosis due to cytomegalovirus infection. Medical Expenses and Medical Allowance were not paid because the drug was administered before April 1, 2015, when the drug was still considered inapplicable for relief benefits.

(3) Cases where necessary tests were 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. Precautions have been issued to healthcare professionals regarding the following relatively common issues: "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. The following presents details of cases where the method of use is not considered proper other than the above.

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

<Case 1> Death due to haemorrhagic shock resulting from pancytopenia associated with methotrexate (Methotrexate tablets).

Methotrexate was administered to an elderly patient with a high creatinine value prior to administration. Symptoms such as pyrexia and rash were observed, after which the patient was instructed to discontinue use of the drug due to suspected serious infections and/or allergies. Although the patient continued to consult the hospital multiple times, periodic monitoring such as blood tests was not performed. The patient had pancytopenia which led to haemorrhagic shock and then dead. Relief benefits were not paid as monitoring was not conducted.

Information noted on package inserts
[Warning] Severe adverse reaction may occur in patients with decreased renal function. Patients should be carefully monitored by conducting renal function tests, etc. prior to and during administration of this drug. [Important Precautions] Serious adverse reaction such as bone marrow depression, hepatic/renal function disorder may occur. Patients should be carefully monitored by conducting clinical laboratory tests (blood tests, liver/renal function test, urinary test, etc.) every 4 weeks prior to and during administration of this drug. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

<Case 2> Drug-induced liver injury associated with terbinafine (Terbinafine tablets)

Although the patient consulted the hospital after beginning administration of terbinafine, no liver function tests were conducted for 49 days; therefore, although the patient had drug-induced liver injury, relief benefits were not paid.

Information noted on package inserts
[Warning] Serious liver disorders (hepatic failure, hepatitis, cholestasis, jaundice, etc.), pancytopenia, agranulocytosis, and thrombocytopenia may occur, resulting in fatal outcomes in some cases. Liver function tests and blood tests should be conducted prior to administering the drug. Patients should be carefully monitored for associated symptoms when administering this drug by conducting periodic tests such as liver function tests and blood tests. (Refer to the “Contraindications”, “Important Precautions”, and “Adverse Reaction” section.) Carefully read the package insert when beginning administration of this drug.

(4) 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 reaction, past medications used at other hospitals, etc.

<Case 1> Use of levonorgestrel/ethinyl estradiol (Ange 28 tablets) in a patient who was contraindicated to take oral contraceptive pills

Approximately 2 years after beginning administration of levonorgestrel/ethinyl estradiol, the patient was found to be hypertensive, which is a contraindication, and obese, which is noted in the Careful Administration section, during a general health checkup. The physician continued to administer the drug without recognizing the necessity of conducting clinical

laboratory tests and confirming hypertension. No clinical laboratory tests or blood pressure measurements were taken for approximately 5 years until the patient had cerebral sinus thrombosis and cerebral haemorrhage; therefore, relief benefits were not paid.

Information noted on package inserts [Contraindications] Patients with hypertension (excluding patients with mild hypertension) [Careful Administration] ● Females who are 40 years or older ● Obese females

<Case 2> Use of benzbromarone (Urinorm tablets) in a patient with nephrolithiasis

Benzbromarone was administered to a patient who was confirmed to have nephrolithiasis on the computed tomography (CT) scan; therefore, relief benefits were not paid even though the patient had nephrolithiasis.

Information noted on package inserts [Contraindications] Patients with nephrolithiasis, Patients with severe renal impairment

(5) 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 Salazac Combined Granules which were prescribed by a physician approximately 7 months ago, and subsequently had erythema multiform-type drug eruption. The patient received no relief benefits.

<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, risperidone (Risperdal Tablets) even after a physician gave instructions to discontinue the drug, and subsequently had drug-induced liver injury. The patient received no relief benefits.

6. Information on the Relief System

For details of the Relief System and the Relief System for Infections Acquired through Biological Products, please refer to the PMDA website. (http://www.pmda.go.jp/relief-services/adr-sufferers/0001.html [only available in Japanese language]). Furthermore, materials on the Relief System are also available on the PMDA website, and PMDA encourages use of these materials to disseminate information on the Relief System.

A consultation service is available (including the Relief System for Infections Acquired through 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

Please note that the following cases will not be applicable to receive relief benefits.

A) Cases of adverse health effects resulting from statutory vaccination practice (Relief System for Injury to Health with Vaccination is applicable in accordance with the Preventive Vaccination Law). However, cases of adverse health effects resulting from voluntary vaccinations are applicable for relief benefits under the Relief System.
B) Cases where it is clear who is responsible for 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:
    i. Pharmaceuticals used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (anticancer drugs, immunosuppressants, etc.)
    ii. Pharmaceuticals that do not have the possibility to cause adverse reaction, 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.
    i. Cases where the disorders or disabilities are considered to be unlikely caused by ADR (those that are not considered to be associated with pharmaceuticals).
    ii. 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).

7. 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 relief benefits under the relief systems, even though the adverse health effects are suspected to have been caused by pharmaceuticals.
When adverse reaction occur and healthcare professionals are consulted by their patient about the reaction, healthcare professionals should provide information regarding the Relief Systems to the patient or their family, if the reaction is possibly applicable for the relief benefits. MHLW/PMDA encourages continued cooperation from healthcare professionals in preparing the documents, such as medical certificates, required to claim these relief benefits.

3

Project of the Japan Drug Information Institute in Pregnancy

1. Tasks of the Japan Drug Information Institute in Pregnancy

The MHLW established the Japan Drug Information Institute in Pregnancy (JDIIP) at the National Center for Child Health and Development in October 2005 to provide a variety of drug consultation services to pregnant women and women who wish to become pregnant based on the latest scientific evidence. The JDIIP also investigates pregnancy outcome in consultation clients to establish new evidence. The activities of the JDIIP have been introduced in Pharmaceuticals and medical devices safety information (PMDSI) No. 268, 279, 290, 305, and 316.

[References]
JDIIP website: http://www.ncchd.go.jp/en/index.html
PMDSI No.268: https://www.pmda.go.jp/files/000153737.pdf
PMDSI No.279: https://www.pmda.go.jp/files/000153493.pdf
PMDSI No.290: https://www.pmda.go.jp/files/000153540.pdf
PMDSI No.305: https://www.pmda.go.jp/files/000153659.pdf
PMDSI No.316: https://www.pmda.go.jp/files/000153674.pdf

2. Cooperating medical institutions

The system for consultation services and prompt information collection of the JDIIP was strengthened in FY 2015, by receiving the cooperation of 5 hospitals (Hirosaki University Hospital, Toyama University Hospital, Japanese Red Cross Society Wakayama Medical Center, Tottori University Hospital, and Japanese Red Cross Kumamoto Hospital) newly joined, in order to enhance the accessibility. The cooperating hospitals are introduced below. (Page 18-23)

3. To all healthcare professionals

Healthcare professionals are encouraged to introduce the consultation services of JDIIP to pregnant women, etc. who are concerned about the effects of drugs they have used during pregnancy.

- Consultation services and procedure:
  http://www.ncchd.go.jp/kusuri/process/index.html

4. The 10th Anniversary Forum of the JDIIP

The JDIIP held a 10th anniversary forum in Tokyo on November 3, 2015. Approximately 500 participants including physicians and pharmacists working in clinical practice as well as government and pharmaceutical company employees attended the forum.

At this forum, the president of the JDIIP introduced medical issues related to use of drugs during pregnancy, background to the establishment of the JDIIP to solve such issues, and the performance of the JDIIP in the past 10 years. The Director of the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, also mentioned deliberating

use of information accumulated in the JDIIP database for revisions of package inserts as a future vision in expanding the JDIIP's operations.

Moreover, experts in various fields gave educational lectures on 2 topics: "Pharmacological treatment during pregnancy and breast-feeding" and "Current status and issues in mental health during pregnancy and puerperium." These were followed by a seminar on "How JDIIP can contribute to treatment guidelines for pregnancy." This seminar covered topics on "How clinical guidelines are created," "Pregnancy in patients with renal diseases," "Pregnancy in patients with Inflammatory Bowel Disease (IBD)", "Safety of drug administration during pregnancy and lactation in patients with renal diseases and IBD", and "Guidelines on obstetrics and [Pregnancy and Drugs]." In addition to introducing basic flow of clinical guideline preparations, precautions related to pregnant women with underlying renal diseases, benefits of providing pharmacological treatment to pregnant patients with IBD, evidence related to administration of drugs in pregnant women for the treatment of renal diseases and IBD, latest information related to pregnancy/breast-feeding and drugs, and current guidelines, discussions were held on how each specialty can be involved in the future management guidelines for pregnancy.

List of Cooperating Medical Institutions in 2015

	Name of medical institution	Contact information, reception hours, etc.
1	Japan Drug Information Institute in Pregnancy	2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 inside the National Center for Child Health and Development TEL: (+81)-3-5494-7845 Reception hours: 10:00 – 12:00, 13:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.ncchd.go.jp/kusuri/index.html
Cooperating Medical Institutions (◎: Joined since 2015)		
2	Hokkaido University Hospital	Kita 14, Nishi 5, Kita-ku, Sapporo-city, Hokkaido 060-8648 TEL: (+81)-11-706-3455 (Please ask for "Outpatient service for pregnancy and drugs") FAX: (+81)-11-706-7616 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
3 ◎	Hirosaki University Hospital	53 Honcho, Hirosaki-city, Aomori 036-8563 TEL: (+81)-172-33-5111 (Extension 6748) Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
4	Iwate Medical University Hospital	19-1 Uchimaru, Morioka-city, Iwate 020-8505 TEL: (+81)-19-624-5263 (Pregnancy and drugs counseling desk: Direct line) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
5	Tohoku University Hospital	1-1 Seiryo-machi, Aoba-ku, Sendai-city, Miyagi 980-8574 TEL: (+81)-22-717-7000 (Hospital's main switchboard number) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.hosp.tohoku.ac.jp/
6	Fukushima Medical University Hospital	1 Hikarigaoka, Fukushima-city, Fukushima 960-1295 TEL: (+81)-24-547-1226 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) HP: http://www.fmu.ac.jp/
7	Tsukuba University Hospital	2-1-1 Amakubo, Tsukuba-city, Ibaraki 305-8576 TEL: (+81)-29-896-7171

		FAX: (+81)-29-896-7170 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
8	Maebashi Red Cross Hospital	3-21-36 Asahi-cho, Maebashi-city, Gunma 371-0014 TEL: (+81)-27-224-4585 (Division of Pharmacy: Extension 7709) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.maebashi.jrc.or.jp/
9	Saitama Medical University Hospital	38 Morohongo Moroyama-machi, Iruma-gun, Saitama 350-0495 TEL: (+81)-49-276-1297 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 15:00 – 17:00 (Monday to Saturday, excluding national holidays)
10	Chiba University Hospital	1-8-1 Inohana, Chuo-ku, Chiba-city, Chiba 260-8677 TEL: (+81)-43-226-2628 (Drug Information, Division of Pharmacy) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
11	Toranomon Hospital	2-2-2 Toranomon, Minato-ku, Tokyo 105-8470 TEL: (+81)-3-3588-1111 (Extension 3410) FAX: (+81)-3-3505-1764 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
12	St. Luke’s International Hospital	9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560 TEL: (+81)-3-5550-2412 FAX: (+81)-3-5550-2563 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
13	Yokohama City University Hospital	3-9 Fukuura, Kanazawa-ku, Yokohama-city, Kanagawa 236-0004 TEL: (+81)-45-787-2800 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.fukuhp.yokohama-cu.ac.jp/
14	Niigata University Medical & Dental Hospital	1-754 Asahimachi-dori, Chuo-ku, Niigata-city, Niigata 951-8520 TEL: (+81)-25-227-2895 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-25-227-2791 Reception hours: 13:30 – 16:00 (Monday to Friday, excluding national holidays)
15	Shinshu University Hospital	3-1-1 Asahi, Matsumoto-city, Nagano 390-8621 TEL: (+81)-263-37-3022 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-263-37-3072 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
16 ◎	University of Toyama Hospital	2630 Sugitani, Toyama-city, Toyama 930-0194 TEL: (+81)-76-434-7863 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)

17	National Hospital Organization Kanazawa Medical Center	1-1 Shimoishibiki-machi,Kanazawa-city, Ishikawa 920-8650 TEL: (+81)-76-262-4161 Reception hours: 9:00 – 16:30 (Monday to Friday, excluding national holidays) URL: http://www.kanazawa-hosp.jp/pv/preg.htm
18	Hamamatsu University Hospital	1-20-1 Handayama, Higashi-ku, Hamamatsu-city, Shizuoka 431-3192 TEL: (+81)-53-435-2637 (Regional Cooperation Unit) FAX: (+81)-53-435-2849 Reception hours: 8:30 – 18:00 (Monday to Friday, excluding national holidays and yearend/new-year) URL: http://www.hama-med.ac.jp/hos_index.html
19	National Hospital Organization Nagara Medical Center	1300-7 Nagara, Gifu-city, Gifu 502-8558 TEL: (+81)-58-232-7755 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-58-295-0077 Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays)
20	Japanese Red Cross Nagoya Daiichi Hospital	3-35 Michishita-cho, Nakamura-ku, Nagoya-city, Aichi 453-8511 TEL: (+81)-52-481-5111 (Division of Pharmacy: Extension 38167) FAX: (+81)-52-482-7733 Reception hours: 13:00 – 16:00 (Monday to Friday, excluding national holidays)
21	Mie University Hospital	2-174, Edobashi, Tsu-city, Mie 514-8507 TEL: (+81)-59-231-5552 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 8:30 – 16:00 (Monday to Friday, excluding national holidays)
22	University Hospital, Kyoto Prefectural University of Medicine	465 Kajii-cho, Hirokoji agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto-City, Kyoto 602-8566 TEL: (+81)-75-251-5862 (Drug Information, Division of Pharmacy) FAX: (+81)-75-251-5859 (same as above): Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
23	Osaka Medical Center and Research Institute for Maternal and Child Health	840 Murodo-cho, Izumi-city, Osaka 594-1101 TEL: (+81)-725-56-5537 (Outpatient department for pregnancy and drugs) Reception hours: 10:00 – 12:00, 14:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.mch.pref.osaka.jp/hospital/department/pharmacy/pharmacy03.html
24	Kobe University Hospital	7-5-2 Kusunoki-cho, Chuo-ku, Kobe-city, Hyogo 650-0017 TEL: (+81)-78-382-5111 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours:13:00 – 17:00 (Monday to Friday, excluding national holidays)
25	Nara Medical University Hospital	840 Shijo-cho, Kashihara-city, Nara 634-8522 TEL: (+81)-744-22-3051 (Division of Pharmacy: Extension 3565) FAX: (+81)-744-29-8027 Reception hours: 8:30 – 16:00

		(Monday to Friday, excluding national holidays) URL: http://www.naramed-u.ac.jp/hospital/shinryoka-bumon/senmongairai/ninshintokusuri.html
26 ◎	Japanese Red Cross Society Wakayama Medical Center	4-20 Komatsubaradori, Wakayama-city, Wakayama 640-8558 TEL: (+81)-73-421-8175 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www2.kankyo.ne.jp/nisseki-w/
27 ◎	Tottori University Hospital	36-1 Nishi-cho, Yonago, Tottori 683-8504 TEL: (+81)-859-38-6642 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 16:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www2.hosp.med.tottori-u.ac.jp/departments/medical/women/17381.html
28	National Hospital Organization Okayama Medical Center	1711-1 Tamasu, Kita-ku, Okayama-city, Okayama 701-1192 TEL: (+81)-86-294-9556 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-86-294-9557 Reception hours: 8:30 – 18:00 (Monday to Friday, excluding national holidays) URL: http://okayamamc.jp/04_bumon/04-04_bumon/04-04_03-02yakuzai.html
29	Hiroshima University Hospital	1-2-3 Kasumi, Minami-ku, Hiroshima-city, Hiroshima 734-8551 TEL: (+81)-82-257-5079 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
30	National Hospital Organization Shikoku Medical Center for Children and Adults	2-1-1 Senyu-cho, Zentsuji-city, Kagawa 765-8507 TEL: (+81)-877-62-1000 FAX: (+81)-877-62-6311 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
31	Tokushima University Hospital	2-50-1 Kuramoto-cho, Tokushima-city, Tokushima 770-8503 TEL: (+81)-70-6586-0831 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
32	Kyushu University Hospital	3-1-1 Maidashi, Higashi-ku, Fukuoka-city, Fukuoka 812-8582 TEL: (+81)-92-642-5900 Reception hours: 14:00 – 17:00 (Monday to Friday, excluding national holidays)
33 ◎	Japanese Red Cross Kumamoto Hospital	2-1-1 Nagamineminami, Kumamoto-city Higashi-ku, Kumamoto 861-8520 TEL: (+81)-96-384-2111 (Extension for Outpatient services for the obstetrics and gynecology department: 6240) (Please ask for “Appointments for outpatient service for pregnancy and drugs”) Reception hours: 14:00 – 16:00 (Monday to Friday, excluding national holidays)
34	University of Miyazaki Hospital	5200 Kihara, Kiyotake-cho, Miyazaki-city, Miyazaki 889-1692

		TEL: (+81)-985-85-1512 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays) URL: http://www.med.miyazakiu.ac.jp/home/hospital/outpatient/5008/
35	Kagoshima City Hospital	20-17 Kajiya-cho, Kagoshima-city, Kagoshima 892-8580 TEL: (+81)-99-224-2101 (Pharmacy department: Extension 2603) (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-99-224-9916 Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)
36	Okinawa Chubu Hospital	281 Miyazato, Uruma-city, Okinawa 904-2293 TEL: (+81)-98-973-4111 (Please ask for “Outpatient service for pregnancy/breastfeeding and drugs”) Reception hours: 13:00 – 16:00 (Tuesday, Thursday, and Friday, excluding national holidays)

4

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 20, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Asunaprevir and daclatasvir hydrochloride

Brand name (name of company)	Asunaprevir: Sunvepra Capsules 100 mg (Bristol-Myers K.K.) Daclatasvir hydrochloride: Daklinza Tablets 60 mg (Bristol-Myers K.K.)
Therapeutic category	Antivirals
Indications	Improvement of viremia in patients with serogroup 1 (genotype 1) chronic hepatitis C or compensated cirrhosis type C

PRECAUTIONS (underlined parts are revised)

Adverse reaction (clinically significant adverse reaction)

Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, or serum marker test should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference information

The number of reported adverse reaction (for which a causality to the drug could not be ruled out) for the past year (from initial marketing to August 2015).

Cases of adverse reaction associated with interstitial pneumonia: 4 cases* (no fatal case)

*Cases for which a causality to combination therapy of asunaprevir and daclatasvir hydrochloride could not be ruled out

The number of patients using this drug estimated by the MAH: Approximately 45 600 (from initial marketing to August 2015)

Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Compensated cirrhosis type C (Hypertension, hypothyroidism, insomnia)	Daklinza Tablets 60 mg and Sunvepra Capsules 200 mg for 98 days	**Interstitial pneumonia** No history of prior treatment. No previous medical history. Day 1 of administration: Combination therapy with Daklinza Tablets 60 mg once daily and Sunvepra Capsules 100 mg twice daily was started. Day 62 of administration: Onset of coughs. Day 77 of administration: Coughs continued. The patient tested positive for pulmonary rales. Slight ground-glass opacities were

				confirmed in bilateral lower lung fields on the chest CT scan. Bronchial asthma was suspected, and administration of salmeterol xinafoate/ fluticasone propionate was started as a symptomatic treatment, after which the patient was monitored. Day 84 of administration: Coughs and rales were resolving. Day 92 of administration: The patient had exertional dyspnoea. Day 98 of administration (day of discontinuation): Coughs and sputum worsened, and pulmonary rales were relapsed. Exacerbation of the ground-glass opacities were confirmed on the chest CT scan. Sialylated carbohydrate antigen KL-6 increased to 3 285 U/mL, and the patient was diagnosed with drug-induced interstitial pneumonia. Administration of Daklinza Tablets and Sunvepra Capsules was discontinued. 1 day after discontinuation: Administration of oral prednisolone (25 mg/day) was started. 3 days after discontinuation: The patient was admitted to the hospital for treatment of drug-induced interstitial pneumonia. 8 days after discontinuation: Intravenous drip administration of ceftriaxone sodium hydrate was started due to suspicions that it may be infectious pneumonia (The drug was administered for 10 days). 15 days after discontinuation: Coughs and sputum were resolving. The patient did not have pyrexia. Dosage of prednisolone was decreased to 20 mg/day. 17 days after discontinuation: KL-6 was 2 619 U/mL. 36 days after discontinuation: Coughs and sputum became mild. Dosage of prednisolone was decreased to 15 mg/day. 40 days after discontinuation: The patient was discharged from the hospital. 49 days after discontinuation: The patient still had mild coughs, but no sputum. 50 days after discontinuation: Dosage of prednisolone was decreased to 10 mg/day. 86 days after discontinuation: Dosage of prednisolone was decreased to 5 mg/day. 140 days after discontinuation: Interstitial pneumonia shadow was resolving on chest CT scans. The patient still had mild coughs. 147 days after discontinuation: Administration of prednisolone was ceased. 170 days after discontinuation: Although cough symptoms exacerbated, chest CT scans showed no changes in image. KL-6 was 776 U/mL and was resolving further. Drug-induced interstitial pneumonia was resolving.

Laboratory examination

	62 days before administration	1 day before administration	Day 28 of administration	Day 77 of administration	Day 84 of administration	Day 98 of administration (Day of discontinuation)
AST (IU/L)	101	103	45	42	54	41
ALT (IU/L)	88	65	43	25	35	24
T-Bil (mg/dL)	1.0	0.9	0.8	0.9	1.7	1.1
LDH (IU/L)	246	269	196	-	217	-
ALB (g/dL)	4.0	4.0	4.1	-	4.1	-
WBC (/mm^3)	4 070	4 400	4 600	5 800	4 410	3 900
Eos (%)	-	-	7.6	-	2	-
CRP (mg/dL)	-	-	-	<=0.05	-	0.1
KL-6 (U/mL)	-	-	-	-	-	3 285
HCV RNA (IU/mL)	7.0	-	Not detected	-	Not detected	-

	3 days after discontinuation	16 days after discontinuation	49 days after discontinuation	77 days after discontinuation	108 days after discontinuation	170 days after discontinuation
AST (IU/L)	35	26	32	33	35	28
ALT (IU/L)	21	26	28	32	37	20
T-Bil (mg/dL)	0.6	0.4	1.2	1.0	0.8	1.3
LDH (IU/L)	221	161	213	232	185	170
ALB (g/dL)	4.1	4.1	4.3	4.3	4.2	4.1
WBC (/mm^3)	4 700	5 960	5 170	5 750	4 730	4 000
Eos (%)	-	0.8	0.2	-	-	-
CRP (mg/dL)	<=0.05	<=0.05	<=0.05	<=0.05	-	0.19
KL-6 (U/mL)	-	-	1 301	1 397	1 105	776
HCV RNA (IU/mL)	-	Not detected	Not detected	Not detected	Not detected	Not detected

Concomitant medications: amlodipine besilate, indapamide, levothyroxine sodium hydrate, etizolam, lansoprazole

5

Revision of Precautions (No. 269)

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 October 20, 2015.

1

Miscellaneous central nervous system agents

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/L (Janssen Pharmaceutical K.K.)
Adverse Reaction (Clinically significant adverse reaction)	**Rhabdomyolysis**: Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feeling of weakness, increased creatine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

2

Miscellaneous hormones

Dutasteride

Brand name	Avolve Capsules 0.5 mg (GlaxoSmithKline K.K.), Zagallo Capsules 0.1 mg, 0.5 mg (GlaxoSmithKline K.K.)
Adverse Reaction (Clinically significant adverse reaction)	**Hepatic function disorder, jaundice**: Hepatic function disorder or jaundice associated with increased levels of AST (GOT), ALT (GPT), bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

3

Antibiotics acting mainly on gram-positive and gram-negative bacteria

Ceftriaxone sodium hydrate

Brand name	Rocephin Intravenous Injections 0.5 g, 1 g, Rocephin Intravenous Infusions Bag 1 g (Chugai Pharmaceuticals), and the others
Adverse Reaction (Clinically significant adverse reaction)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and acute generalised exanthematous pustulosis**: Toxic epidermial necrolysis, oculomucocutaneous syndrome, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

4

Antibiotics acting mainly on gram-positive bacteria and mycoplasma

Roxithromycin

Brand name	Rulid Tablets 150 (Sanofi K.K.) and the others
Careful Administration	Patients with risk of prolonged QT (patients with congenital long QT syndrome, patients with abnormal electrolytes such as hypokalemia, and patients who are receiving drugs known to cause prolonged QT)
Adverse Reaction (Clinically significant adverse reaction)	**Pseudomembranous colitis, haemorrhagic colitis**: Serious colitis such as pseudomembranous colitis or haemorrhagic colitis may occur. If abdominal pain, frequent diarrhea, or bloody stool is observed, appropriate measures such as immediate discontinuation of administration should be adopted. **QT prolonged, ventricular tachycardia (including torsades de pointes)**: Prolonged QT or ventricular tachycardia (including torsades de pointes) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

5

Laxatives

Laxative drug containing magnesium oxide (Over the counter drugs)

Brand name	Slaria Laxative (ROHTO Pharmaceutical Co., Ltd.) and the others
Consultation	The following persons should contact a physician, pharmacist, or registered salesperson for a consultation before administration. The elderly.

6

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 October 31, 2015)

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
ciprofloxacin Ciproxan I.V. 200 mg[*1]	Bayer Yakuhin, Ltd.	September 24, 2015
lamotrigine Lamictal Tablets for Pediatric Use 2 mg, 5 mg, Lamictal Tablets 25 mg, 100 mg[*2]	GlaxoSmithKline K.K.	September 24, 2015
rivaroxaban Xarelto Tablets 10 mg, 15 mg[*3]	Bayer Yakuhin, Ltd.	September 24, 2015
olanexidine gluconate (1) Olanedine Antiseptic Solution 1.5% (2) Olanedine Solution 1.5% Antiseptic Applicator 10 mL (3) Olanedine Solution 1.5% Antiseptic Applicator 25 mL	Otsuka Pharmaceutical Co., Ltd.	September 16, 2015
dulaglutide (genetical recombination) Trulicity Ateos Subcutaneous Injection 0.75 mg	Eli Lilly Japan K.K.	September 16, 2015
collagenase (clostridium histolyticum) Xiaflex Injection	Asahi Kasei Pharma Corporation	September 16, 2015
antithrombin gamma (genetical recombination) Acoalan Injection 600	Kyowa Hakko Kirin Co., Ltd.	September 7, 2015
hydroxychloroquine sulfate Plaquenil Tablets 200 mg	Sanofi K.K.	September 7, 2015
insulin glargine (genetical recombination) Lantus XR Injection SoloStar	Sanofi K.K.	September 7, 2015
ledipasvir acetonate/sofosbuvir Harvoni Combination Tablets	Gilead Sciences, Inc.	September 1, 2015
talaporfin sodium Laserphyrin 100 mg Injection[*4]	Meiji Seika Pharma Co., Ltd.	September 1, 2015
eliglustat tartrate Cerdelga Capsule 100 mg	Genzyme Japan K.K.	September 1, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
nintedanib ethanesulfonate Ofev Capsules 100 mg, 150 mg	Nippon Boehringer Ingelheim Co., Ltd.	August 31, 2015
panobinostat lactate Farydak Capsules 10 mg, 15 mg	Novartis Pharma K.K.	August 31, 2015
ipilimumab (genetical recombination) Yeryov Injection 50 mg	Bristol-Myers K.K.	August 31, 2015
asfotase alfa (genetical recombination) Strensiq Subcutaneous Injection 12 mg/0.3 mL, 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/1 mL, 80 mg/0.8 mL	Alexion Pharma G.K.	August 31, 2015
catridecacog (genetical recombination) NovoThirteen Intravenous Injections 2 500	Novo Nordisk Pharma Ltd.	August 27, 2015
nitric oxide INOflo for Inhalation 800 ppm[*5]	Air Water Inc.	August 24, 2015
bosentan hydrate Tracleer Tablets 62.5 mg[*6]	Actelion Pharmaceuticals Japan Ltd.	August 24, 2015
ribavirin Rebetol Capsules 200 mg[*7]	MSD K.K.	July 29, 2015
clindamycin phosphate hydrate/benzoyl peroxide Duac Combination Gel	GlaxoSmithKline K.K.	July 17, 2015
gadobutrol Gadovist IV Injection 1.0 mol/L Syringe 5 mL, 1.0 mol/L Syringe 7.5 mL, 1.0 mol/L Syringe 10mL	Bayer Yakuhin, Ltd.	June 30, 2015
bortezomib Velcade Injection 3 mg[*8]	Janssen Pharmaceutical K.K.	June 26, 2015
lidocaine/propitocaine EMLA Cream[*9]	Sato Pharmaceutical Co., Ltd.	June 26, 2015
edaravone Radicut Injection 30 mg, Radicut Bag for I.V. Infusion 30 mg[*10]	Mitsubishi Tanabe Pharma Corporation	June 26, 2015
botulinum toxin type A Botox for Injection 50 units, 100 units[*11]	GlaxoSmithKline K.K.	June 26, 2015
tazobactam/piperacillin hydrate Zosyn IV Injection 2.25 and 4.5, Zosyn Fixed-dose Bag for I.V. Infusion 4.5[*12]	Taiho Pharmaceutical Co., Ltd.	June 26, 2015
pitavastatin calcium hydrate Livalo Tablets 1 mg and 2 mg, Livalo OD Tablets 1 mg and 2 mg[*13]	Kowa Company, Ltd.	June 26, 2015
ramucirumab (genetical recombination) Cyramza Injection 100 mg, 500 mg	Eli Lilly Japan K.K.	June 22, 2015
macitentan Opsumit Tablets 10 mg	Actelion Pharmaceuticals Japan Ltd.	June 9, 2015
tramadol hydrochloride Onetram Tablets 100 mg	Nippon Shinyaku Co., Ltd.	June 2, 2015
trelagliptin succinate Zafatek Tablets 50 mg, 100 mg	Takeda Pharmaceutical Company Limited	May 28, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
peginterferon alfa-2b (genetical recombination) Peginteron Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL	MSD K.K.	May 26, 2015
ramosetron hydrochloride Irribow Tablets 2.5 μg and 5 μg[*15], Irribow OD Tablets 2.5 μg and 5 μg[*15]	Astellas Pharma Inc.	May 26, 2015
duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg[*16]	Shionogi & Co., Ltd.	May 26, 2015
nalfurafine hydrochloride Nopicor Capsules 2.5 μg[*17]	Toray Medical Co., Ltd.	May 26, 2015
aripiprazole hydrate Abilify prolonged release aqueous suspension for IM injection 300 mg and 400 mg, Abilify prolonged release aqueous suspension for IM injection 300 mg Syringe and 400 mg Syringe	Otsuka Pharmaceutical Co., Ltd.	May 25, 2015
colistin sodium methanesulfonate Aldreb for Injection 150 mg	GlaxoSmithKline K.K.	May 25, 2015
(1) sofosbuvir, (2) ribavirin (1) Sovaldi Tablets 400 mg, (2) Copegus Tablets 200 mg[*18]	(1) Gilead Sciences, Inc. (2) Chugai Pharmaceutical Co., Ltd.	May 25, 2015
pomalidomide Pomalyst Capsules 1 mg, 2 mg, 3 mg, 4 mg	Celgene K.K.	May 21, 2015
nalfurafine hydrochloride Remitch Capsules 2.5 μg	Toray Industries, Inc.	May 20, 2015
lenvatinib mesilate Lenvima Capsules 4 mg, 10 mg	Eisai Co., Ltd.	May 20, 2015
aclidinium bromide Eklira 400 μg Genuair 30, 400 μg Genuair 60	Kyorin Pharmaceutical Co., Ltd.	May 20, 2015
4-strain meningococcal vaccine (diphtheria toxoid conjugate) Menactra intramuscular injection	Sanofi K.K.	May 18, 2015
metronidazole Rozex Gel 0.75%	Galderma S.A.	May 11, 2015

*1 Pediatric indication and dosage

*2 Typical absence seizures

*3 Treat deep-vein thrombosis (DVT) and pulmonary embolism, and prevent DVT and pulmonary embolism from relapse

*4 Localized, residual recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy

*5 Improvement of pulmonary hypertension in the perioperative period of cardiac surgery

*6 Suppress development of digital ulcers in systemic sclerosis (scleroderma)

*7 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir

*8 Mantle cell lymphoma

*9 Pediatric dose for pain relief during skin laser therapy and indications for pain relief during pricking injection of an intravenous indwelling needle

*10 Suppress progression of functional disorders associated to amyotrophic lateral sclerosis (ALS)

*11 Strabismus
*12 Febrile neutropenia (new pediatric dose)
*13 Familial hypercholesterolemia (new pediatric dose)
*14 Postoperative adjuvant therapy for malignant melanoma
*15 Irritable bowel syndrome with diarrhoea in females
*16 Pain associated with fibromyalgia
*17 Improvement of pruritus in patients with chronic liver disease
*18 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir
*19 Improvement of pruritus in patients with chronic liver disease