Pharmaceuticals and Medical Devices Safety Information

No. 330 February 2016

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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 () 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. 330 February 2016

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

[Outline of Information]

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 MAH. 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
Al-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CRP	C-reactive protein
CT	Computed tomography
DVT	Deep vein thrombosis
ELD	Evaluation and Licensing Division
EPPV	Early post-marketing phase vigilance
GAD	General Affairs Division
HPB	Health Policy Bureau
INR	International normalized ratio
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PE	Pulmonary embolism
PEHB	Pharmaceutical and Environmental Health Bureau
PFSB	Pharmaceutical and Food Safety Bureau
PT	Prothrombin time
SD	Safety Division
SP-D	Surfactant protein-D
SpO_2	Oxygen saturation
WBC	White blood cell count
X-P	X-ray photograph
γ-GTP	Gamma-glutamyl transpeptidase

1

Preventative Measures for Accidental Ingestion of Pharmaceuticals by Children

1. Introduction

Many accidental ingestions of pharmaceuticals by children have been reported in surveys conducted by the Consumer Safety Investigation Committee, etc. (Refer to [Reference Materials] on recent investigative reports). There have also been reports of such children being hospitalized due to serious toxic symptoms from accidental ingestion of psychotropic drugs, etc. Furthermore, in the notification from the MHLW, “2013 Hospital monitoring reports on health hazards related to household products”, dated March 2015, the number of accidental ingestions of “pharmaceuticals/quasi-drugs” exceeded that for “tobacco” and became Number 1 in terms of household hazards.

In order to prevent accidental ingestion of pharmaceuticals by children, this section will introduce the requests currently made to healthcare related professionals.

2. Background of accidental ingestions

Based on the various recent investigative reports, accidental ingestions often occur in children aged 1 to 2 years old, especially because children at this age are able to open packages and remove drugs on their own. As a result of improper storage of pharmaceuticals being left on top of the table or shelf, etc., and many accidental ingestions among children occur while guardians’ are not looking.

The accidental ingestions of ethical pharmaceuticals is higher for pharmaceuticals prescribed to other family members or relatives than for pharmaceuticals prescribed to children themselves.

In addition, accidental overdose of orally-disintegrating tablets with a sweet flavor have been recently reported. Pharmaceuticals such as syrups flavored so that children can easily swallow it are thought to be tasteful for children, and there have been reports that it is not unusual to accidentally ingest it by taking it out of the refrigerator on their own even after it is properly stored by guardians.

Furthermore, based on a survey conducted among guardians whose children accidentally ingested pharmaceuticals (conducted by the Consumer Safety Investigation Committee), approximately 60% of respondents stated that they have never received instructions to be cautious about accidental ingestion of pharmaceuticals by children or did not remember receiving such instructions. The fact that accidental ingestions are not well recognized, and the fact that there have been many reports of guardians being unaware of how to handle such accidents when they occur. Such backgrounds are possible causes of such accidents.

3. Accidental ingestions based on children’s behavioral characteristics

Over 90% of accidental ingestions of pharmaceuticals by children occur at home, and tend to occur among children starting from approximately 6 months old when children are prone to put anything nearby in their mouth.

Accidental ingestions are influenced by behavioral characteristics of children which change depending on age and developmental stage, such as “being prone to place anything

nearby in their mouth," "becoming highly interested in their surroundings and copying those whom interest them," and "becoming curious and picking things up based on preference."

As a result, it is effective to specifically describe to guardians, etc. as mentioned in the following points, characteristics of accidents prone to occur depending on the child's growth, cautionary points, and types of pharmaceuticals they should especially be cautious about.

1 "Being prone to place anything nearby in their mouth

Many accidental ingestions occurred among children aged approximately 6 months to 1 and a half years old because of their behavior of picking nearby things up and placing it in their mouth.

- Accidentally ingest pharmaceuticals which you would not expect to place in the mouth, such as topical drugs.
- Have a tendency to accidentally ingest pharmaceuticals in unusual ways such as placing the entire package in their mouth and chewing on it, chewing on the package and breaking it, and biting on metal tubes.

2 "Becoming highly interested in their surroundings and copying those whom interest them"

Children aged 1 year old (especially at around 1 and a half years old) to 2 years old become interested in their surroundings and may accidentally ingest pharmaceuticals because they copy their guardians.

There were many reports of:

- Children reaching for pharmaceuticals in high places by using extra footing.
- Accidental ingestion of pharmaceuticals for adults.
- Ingestion of pharmaceuticals by removing it from the package in the normal way.

3 "Becoming curious and picking things up based on preference"

Children who are 2 years old or older have a tendency to pick things up due to curiosity and do so using tools since their hands and feet as well as their brain develops further. In such cases, children accidentally ingest pharmaceuticals due to curiosity towards such items.

- Accidentally ingest large quantities of liquid medicine with a sweet flavor.
- Accidentally ingest large quantities of chewable, drops, or jelly formulations since they mistake the pharmaceuticals with sweets.

*Investigative report on causes of accidents, etc. based on Article 23-1 of the Consumer Safety Act "Accidental Ingestion of Pharmaceuticals by Children" (From the Consumer Safety Investigation Committee dated December 18, 2015)

4. How to handle occurrences of accidental ingestion

Even if accidental ingestion occurs, risk of the incident becoming severe decreases if rapid and proper measures are taken.

If, by any chance, accidental ingestion occurs, please contact a specialized consulting organization immediately or consult a medical institution as necessary after confirming the child's state, name of the drug ingested, and the amount ingested. Consulting organizations for accidental ingestion include "Children's emergency telephone consultation (#8000)" and "Poison 110 telephone number at the Japan Poison Information Center." Furthermore, in order to effectively consult such organizations and obtain precise responses, it is important to accurately describe the name of the drug ingested, the amount ingested, how the incident occurred, etc.

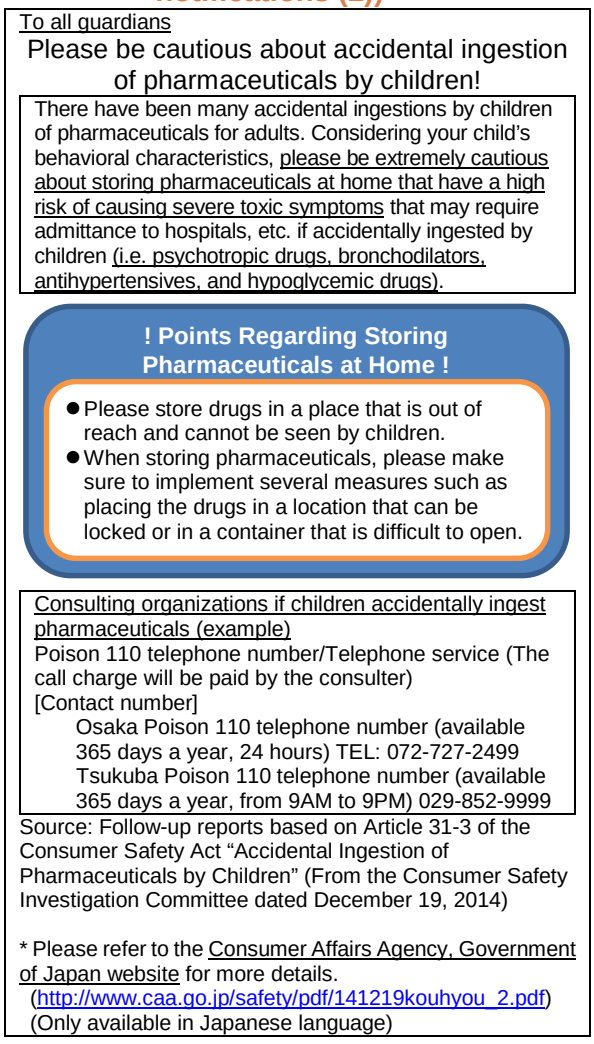
(Consulting organization: example)
(1) “Children’s emergency telephone consultation”
Contact number: #8000
* By pushing the abbreviated phone number consistent nationwide (#8000), you are automatically transferred to the consulting office of the prefecture you currently live in.
(2) “Poison 110 telephone number at the Japan Poison Information Center (For general use)”
Contact number:
- Osaka Poison 110 telephone number (available 365 days a year, 24 hours) 072-727-2499 (Fee for provision of information: Free)
- Tsukuba Poison 110 telephone number (available 365 days a year, from 9AM to 9PM) 029-852-9999 (Fee for provision of information: Free)

5. Requests to healthcare professionals

Given such circumstances, the MHLW issued notifications (refer to [Reference] Related notifications (2) and (3)), and healthcare professionals are encouraged to proactively alert and provide information to patient’s family members, etc. by presenting relevant information (refer to **Figure 1** below).

1. Please remind guardians to properly store and manage pharmaceuticals such as storing it in places where children cannot reach.
   *Particularly be cautious about pharmaceuticals which are accidental ingestion is associated with high risk of developing severe toxic symptoms (i.e. psychotropic drugs, bronchodilators, antihypertensives, and hypoglycemic drugs).
   *It is important to also implement measures such as indicating cautionary points regarding accidental ingestion by children on drug packages, etc.
   *Alert caregivers such as family members if the patient is elderly, etc. and unable to properly store/manage pharmaceuticals themselves.
2. Provide information on how to deal with accidental ingestions when they occur by providing examples of consulting organizations and information required when consulting such organizations.

Figure 1: Example of presented information (from Related notifications (2))



6. Measures related to packaging containers

Recently, it has been found that child-resistant containers are effective in preventing accidents.

Currently, these are being deliberated by the "Research regarding evaluation of packaging containers to prevent accidental ingestion of pharmaceuticals by children" funded by the Health and Labour Sciences Research Grant. Based on the results, preventative measures for such accidental ingestions including use of packaging containers are scheduled to be implemented in the future (refer to [Reference] Related notifications (1)); however, appropriate management of storing pharmaceuticals considering the presence of children in the house is extremely important.

In order to prevent accidental ingestion of pharmaceuticals by children, healthcare professionals are encouraged to proactively alert and provide information to patient's family members, etc.

[Reference]

Recent investigative reports

1. "Investigative report on causes of accidents, etc. based on Article 23-1 of the Consumer Safety Act "Accidental Ingestion of Pharmaceuticals by Children""
   December 18, 2015 Consumer Safety Investigation Committee
   http://www.caa.go.jp/csic/action/pdf/7_honbun.pdf
   (Overview) http://www.caa.go.jp/csic/action/pdf/7_gaiyou.pdf
   (Only available in Japanese language)
2. "2013 Hospital monitoring reports on health hazards related to household products"
   March 31, 2015 Chemical Safety Office, Evaluation and Licensing Division (ELD), Pharmaceutical and Food Safety Bureau (PFSB), MHLW
   (Report) http://www.mhlw.go.jp/file/04-Houdouhappyou-11123000-Iyakushokuhinkyoku-Shinsakanrika/0000079648.pdf
   (Only available in Japanese language)
3. "Safety measures for pharmaceutical containers mainly regarding liquid medication for children"
   (April 2011 Tokyo Safety Measures Council for Products, etc.)
   https://www.shouhiseikatu.metro.tokyo.jp/anzen/kyougikai/h22/houkoku.html
   (Report)
   https://www.shouhiseikatu.metro.tokyo.jp/anzen/kyougikai/h22/documents/houkokusho_all.pdf
   (Only available in Japanese language)

Related notifications, etc.

1. "Preventative measures for accidental ingestion of pharmaceuticals by children"
   December 18, 2015 Notification from the General Affairs Division (GAD) of the Health Policy Bureau (HPB), GAD of the Pharmaceuticals and Environmental Health Bureau (PEHB), Safety Division (SD) of the PEHB, MHLW
   https://www.pmda.go.jp/files/000208938.pdf
   (Only available in Japanese language)
2. "Thorough implementation of preventative measures for accidental ingestion of pharmaceuticals by children" (Alert caution and request widespread dissemination to medical institutions and pharmacies)
   December 24, 2014 GAD/HPB Notification No. 1224-3, GAD/PFSB Notification No. 1224-1, and SD/PFSB Notification No. 1224-2
   https://www.pmda.go.jp/files/000198337.pdf
   (Only available in Japanese language)

3. “Thorough implementation of preventative measures for accidental ingestion of pharmaceuticals, etc.” (Alert caution and request widespread dissemination to medical institutions and pharmacies)
   January 4, 2013 GAD/HPB Notification No. 0104-1, GAD/PFSB Notification No. 0104-2, and SD/PFSB Notification No. 0104-1
   https://www.pmda.go.jp/files/000146031.pdf
   (Only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated January 12, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Amlodipine besilate

Brand name (name of company)	Norvasc Tablets 2.5 mg, 5 mg, and 10 mg, Norvasc OD Tablets 2.5 mg, 5 mg, and 10 mg (Pfizer Japan Inc.), Amlodin Tablets 2.5 mg, 5 mg, and 10 mg, Amlodin OD Tablets 2.5 mg, 5 mg, and 10 mg (Sumitomo Dainippon Pharma Co., Ltd.), and the others
Therapeutic category	Vasodilators
Indications	Hypertension, angina pectoris

PRECAUTIONS (underlined parts are revised)

Adverse reaction (clinically significant adverse reaction)

Fulminant hepatitis, hepatic function disorder, and jaundice: Fulminant hepatitis, hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, etc. or jaundice 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.

Agranulocytosis, leukopenia, and thrombocytopenia: Agranulocytosis, leukopenia, or thrombocytopenia may occur. Patients should be carefully monitored through clinical laboratory testing, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feeling of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

Reference information

The number of reported adverse reaction (for which a causality to the drug could not be ruled out) for the past 3 years and 7 months (from April 2012 to October 2015).

Cases of fulminant hepatitis: 1 case (which had a fatal outcome)
Cases of adverse reaction associated to agranulocytosis: 1 case (no fatal case)
Cases of adverse reaction associated to rhabdomyolysis: 1 case (no fatal case)

The number of patients using this drug estimated by the MAH: Approximately 4 470 000 (estimation provided by the original drug manufacturer excluding the number of patients using fixed-dose combination products or generics from April 2014 to March 2015)
Launched in Japan: December 1993

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Hypertension (constipation)	5 mg for 25 days	**Fulminant hepatitis, drug eruption** Approximately 6 years before administration: The patient underwent low anterior resection for rectal cancer (stage IIIa). Afterwards, underwent another surgery due to ruptured sutures. A transverse colon stoma was established. Approximately 5 years before administration: Close stoma. 85 days before administration: The patient was admitted to the hospital due to adhesive ileus. 82 days before administration: Small bowel resection was performed. 55 days before administration: The patient was prescribed magnesium oxide, butyric acid bacteria preparation, and *daikenchuto* for constipation, and was then discharged from the hospital. 18 days before administration: Consulted the hospital that prescribed amlodipine besilate with complaints about constipation. Blood pressure was 180-83 mmHg, and the patient was instructed to restrict salt intake and was placed under observation. Day 1 of administration: Initiated treatment with amlodipine besilate due to high blood pressure: 178-94 mmHg. Day 14 of administration: Blood pressure was 132-80 mmHg, and no changes were observed (good progress). No subjective symptoms except slightly soft faeces, and no findings specifically noted. Administration of amlodipine besilate was continued. Day 20 of administration: 3-10mm bulging, urticaria-like rash associated with pruritus found on the patient's neck, both upper extremities, back, and both knees. Day 21 of administration: Consulted the hospital that prescribed amlodipine besilate. Prescribed 20 mL intravenous injection of glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate combination and 10 mg×3/day prednisolone (for 3 days), although the cause of rash cannot be determined. Day 23 of administration: The degree of rash exacerbated; 20 mL intravenous injection of glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate combination and 1 combination tablet×3/day of betamethasone/d-chlorpheniramine maleate (for 3 days) was prescribed, even though the cause of rash was yet to be determined. Blood was collected and sent to a clinical laboratory for testing. Day 25 of administration (day of discontinuation): Hospital received an emergency FAX of the test

				results from the laboratory in the morning. The patient was suspected of suffering from severe liver disorder due to AST levels 2 750 IU/L and ALT levels 724 IU/L. The patient was referred to the hospital that conducted the treatment on the same day. The patient was admitted to the hospital that conducted the treatment. (Findings at admission: Confirmed diffuse erythema on both forearms, abdominal area, and lower back, which was associated with severe itchiness. In addition to liver disorder, prothrombin time (PT) had decreased to 18.4%, and the patient was suspected to be suffering from severe acute hepatitis and drug eruption caused by amlodipine. The patient tested negative for virus markers. The patient was a routine drinker.) Discontinued administration of all oral drugs, and administered prednisolone 30 mg, 40 mL intravenous injection of glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate combination, and 20 mg menatetrenone. 3 days after discontinuation: PT was not resolve, and plasma exchange was initiated on the same day. 4 days after discontinuation: Plasma exchange was conducted. 5 days after discontinuation: Conscious level decreased since the afternoon. Onset of and diagnosed as encephalopathy. 6 days after discontinuation: Conscious level did not resolve and patient was comatose. 7 days after discontinuation: No abnormalities found on head computed tomography (CT). Hepatic atrophy progressed. The patient was initiated on plasma exchange and hemodiafiltration. 8 days after discontinuation: Plasma exchange + hemodiafiltration was conducted, but conditions were not resolved. 9 days after discontinuation: Blood pressure decreased during hemodiafiltration, and it was determined that continuation with treatment was difficult. Urine output decreased after that. 11 days after discontinuation: The patient went into respiratory arrest and died.

Laboratory examination

	60 days before administration	Day 23 of administration	Day 25 of administration	1 day after discontinuation In the morning	1 day after discontinuation In the evening	2 days after discontinuation	3 days after discontinuation
AST (GOT) (IU/L)	21	2 750	1 932	984	670	564	428
ALT (GPT) (IU/L)	21	724	1 076	925	801	845	888
Al-P (IU/L)	218	420	565	416	371	421	520
γ-GTP (IU/L)	-	84	106	81	71	70	71
LDH (IU/L)	166	-	1 504	722	467	478	391
BUN (mg/dL)	9.7	26.8	26.6	14.9	-	8.3	6.0
Creatinine (mg/dL)	0.50	0.66	0.71	0.55	-	0.49	0.45
PT (%)	-	-	18.4	19.0	16.4	17.4	16.6
PT (sec)	-	-	33.5	32.6	36.6	34.9	36.2
PT-INR	-	-	2.85	2.78	3.10	2.96	3.06

	4 days after discontinuation	5 days after discontinuation	6 days after discontinuation	7 days after discontinuation In the morning	7 days after discontinuation In the evening	8 days after discontinuation	9 days after discontinuation
AST (GOT) (IU/L)	228	179	186	81	53	49	75
ALT (GPT) (IU/L)	441	318	483	374	125	113	121
Al-P (IU/L)	387	344	506	412	264	199	214
γ-GTP (IU/L)	50	37	55	51	30	29	29
LDH (IU/L)	371	332	444	389	344	343	377
BUN (mg/dL)	6.8	6.8	11.1	17.5	7.2	15.4	12.1
Creatinine (mg/dL)	0.51	0.46	0.54	0.66	0.36	0.67	0.48
PT (%)	30.4	27.7	17.4	15.1	41.9	10.9	16.0
PT (sec)	22.8	24.6	34.3	37.9	18.2	48.1	36.7
PT-INR	1.98	2.06	2.84	3.12	1.55	3.90	3.00

Concomitant medications: sennoside, magnesium oxide, butyric acid bacteria preparation, *daikenchuto*

2 Itraconazole

Brand name (name of company)	(1) Itrizole Capsules 50 mg (Janssen Pharmaceutical K.K.), and the others (2) Itrizole Oral Solution 1% (Janssen Pharmaceutical K.K.) (3) Itrizole Injections 1% (Janssen Pharmaceutical K.K.)
Therapeutic category	Miscellaneous chemotherapeutics
Indications	(1) <Applicable microorganisms> Dermatophytosis (genus *Trichophyton*, genus *Microsporum*, genus *Epidermophyton*), genus *Candida*, genus *Malassezia*, genus *Aspergillus*, genus *Cryptococcus*, genus *Sporothrix*, and genus *Fonsecaea*. <Indications> ● Visceral mycosis (deep mycosis) Fungaemia, respiratory

	mycosis, gastrointestinal mycosis, urinary tract mycosis, and fungal meningitis. ● Deep cutaneous mycosis Sporotrichosis and chromomycosis ● Superficial cutaneous mycosis (excluding nail tinea) Tinea: Body tinea, tinea cruris, tinea manuum, tinea pedis, tinea capitis, kerion Celsi, and tinea barbae Candidiasis: Oral candidiasis, skin candida, nail candida, candidal paronychia/onychia, candidal sycosis, and chronic mucocutaneous candidiasis. Tinea verisicolour and Malassezia folliculitis ● Nail tinea (2) 1. Fungal infection <Applicable microorganisms> Genus *Aspergillus*, genus *Candida*, genus *Cryptococcus*, genus *Blastomyces*, and genus *Histoplasma*. <Indications> Fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, oropharyngeal candidiasis, oesophageal candidiasis, blastomycosis, and histoplasmosis. 2. Febrile neutropenia suspected to be caused by fungal infection. 3. Prophylaxis for deep mycosis among patients with hematological malignancies or hematopoietic stem cell transplant patients predicted to develop neutropenia. (3) 1. Fungal infection <Applicable microorganisms> Genus *Aspergillus*, genus *Candida*, genus *Cryptococcus*, genus *Blastomyces*, and genus *Histoplasma*. <Indications> Fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, oesophageal candidiasis, blastomycosis, and histoplasmosis. 2. Febrile neutropenia suspected to be caused by fungal infection.

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, 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 5 years and 7 months (from April 2010 to October 2015). Cases of adverse reaction associated to interstitial pneumonia: 2 cases* (no fatal case) * 1 case was for a condition not included in the approved dosage and administration The number of patients using this drug estimated by the MAH: (1) Approximately 52 000 (from June 2014 to May 2015, estimation provided by the original drug manufacturer excluding the number of patients using generics) (2) Approximately 25 000 (from June 2014 to May 2015) (3) Approximately 550 (from June 2014 to May 2015)

Launch in Japan: (1) August 1993
(2) September 2006
(3) December 2006

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Aspergilloma (seasonal allergy)	400 mg injection for 2 days ↓ 200 mg injection for 12 days ↓ 200 mg capsules for 9 days	**Acute lung disorder** The patient has a history of being infected by atypical mycobacteria. Day 1 of administration: Treatment with intravenous infusion of itraconazole 400 mg/day (injection) was initiated for treatment of aspergilloma. Day 3 of administration: The dose of itraconazole (injection) was decreased to 200 mg/day. Day 15 of administration: Switch itraconazole to 200 mg/day (capsule formulation). Day 23 of administration (Day of onset/day of discontinuation): Onset of acute lung disorder. Patient consulted a medical institution due to dyspnoea and malaise. SpO_2 was 91% (room air), and C-reactive protein (CRP) was 16.1. Ground glass opacity were confirmed on the left lung, and the patient was admitted to the hospital. Infusion of panipenem/betamipron was initiated. Ground glass opacity were confirmed on the entire left lung on the chest CT scans as well. 4 days after discontinuation: Continuous pyrexia around 38°C was observed since being admitted to the hospital. SpO_2 was 91% but observed to be 94% after inhalation of 5L oxygen. Since chest X-ray photograph (X-P) and CRP did not resolve, infusion of panipenem/betamipron was switched to infusion of methylprednisolone sodium succinate. 6 days after discontinuation: Pyrexia resolved, but SpO_2 decreased to 83%, and was observed to increase to 94% with inhalation of 5L oxygen using the oxymizer. CRP decreased to 8.0 but chest X-P was not resolved. Infusion of methylprednisolone sodium succinate was switched to infusion of prednisolone sodium succinate. 8 days after discontinuation: Chest X-P was resolving and CRP was 2.7. 11 days after discontinuation: The shadow almost disappeared on the chest X-P. CRP was 1.7. SpO_2 was observed to be 95% to 99% (with a 1L oxygen cannula). 14 days after discontinuation: Infusion of prednisolone sodium succinate was switched to an oral treatment. 15 days after discontinuation: CRP was 0.1, and $Sp0_2$ was observed to be 95% to 99% (with room air). Acute lung disorder resolved.

Laboratory examination

	2 days before administration	1 day before administration	Day 1 of administration	Day 6 of administration	Day 7 of administration	Day 13 of administration	Day 15 of administration	Day 16 of administration	Day 23 of administration (day of onset/ day of discontinuation)	4 days after discontinuation	6 days after discontinuation	8 days after discontinuation	11 days after discontinuation	15 days after discontinuation
Temp (°C)	-	36.9	36.4	-	36.5	36.5	36.4	37.4	-	-	-	-	-	-
WBC (/μL)	5 060	-	-	3 650	-	4 870	-	-	7 010	6 460	-	-	-	-
CRP (mg/dL)	-	-	-	-	-	-	-	-	16.1	-	8.0	2.7	1.7	0.1

Concomitant medications: carbocisteine, dextromethorphan hydrobromide hydrate, rebamipide, cherry bark extract/codeine phosphate hydrate

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Bronchopulmonary aspergillosis (Emphysema, chronic obstructive pulmonary disease)	800 mg for 23 days	**Drug-induced lung disorder** The patient did not have a history of allergies. The patient did not have a family history related to the primary disease or the adverse events. The patient did not have a history of adverse events related to drugs used prior to administration of itraconazole. The patient did have a history of smoking (40 cigarettes/day). 2 days before administration: Found only findings related to the primary disease (i.e. bronchopulmonary aspergillosis) on the X-ray image. Day 1 of administration: Twice daily administration of 400 mg itraconazole (oral solution) was initiated for the treatment of bronchopulmonary aspergillosis. Date unknown: The patient could swallow the drug, but felt discomfort during administration. Day 2 of administration: The patient complained of inappetence, but treatment with itraconazole was continued. The patient was sensitive to taste and strongly complained of bitter taste even after mixing the drug with orange juice. Day 22 of administration (day of onset): Lung image findings deteriorated gradually. Increased inhaled oxygen from 2 L to 4 L. Onset of drug-induced lung disorder. Clinical symptoms of drug-induced lung disorder: coughing, exacerbation of pleural effusion, and increase in amount of oxygen required. Day 23 of administration (day of discontinuation): Multiple shadows were observed on the X-ray, and administration of itraconazole was discontinued as the

				patient was suspected of having drug-induced lung disorder due to this drug. Abnormal findings on chest X-ray: Distribution (bilateral) and shadow (infiltrative shadow). Body temperature was 38.1°C, white blood cell count (WBC) was 6 170, C-reactive protein (CRP) was 4.8, and surfactant protein-D (SP-D) was 9.5. 6 days after discontinuation: Imaging diagnostics were conducted. Although multiple spreads were observed on the CT as well, subjective symptoms were resolving. Abnormal findings on CT scans: Distribution (multiple) and shadow (infiltrative shadow, ground glass opacity). Lung disorder was resolving slightly based on the imaging diagnostics, and amount of oxygen inhaled was gradually decreasing as well. 7 days after discontinuation: Bitter taste and inappetence resolved. 41 days after discontinuation: Recovery was observed on imaging diagnostics as well. Body temperature was 36.7°C. Drug-induced lung disorder resolved. Itraconazole was not administered again.
	Laboratory examination			
	Concomitant medications: torasemide, indacaterol maleate, carbocysteine, caspofungin acetate			

	2 days before administration	Day 13 of administration	Day 16 of administration	Day 22 of administration (day of onset)	Day 23 of administration (day of discontinuation)	11 days after discontinuation	41 days after discontinuation
CRP (mg/dL)	-	2.5	2.8	-	4.8	2.8	-
WBC (/μL)	-	5 410	5 540	-	6 170	8 460	-
Temp (°C)	37.0	-	-	37.2	38.1	-	36.7
SP-D (ng/mL)	-	-	-	-	9.5	-	-

The approved dosage and administration for itraconazole (oral solution) is 20 mL per day (200 mg itraconazole). The maximum dose for 1 administration is 20 mL, and the maximum dosage for 1 day is 40 mL.

3

Revision of Precautions (No. 271)

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 January 12, 2016.

1 Antihypertensives

Azilsartan

Brand name	Azilva Tablets 10 mg, 20 mg, and 40 mg (Takeda Pharmaceutical Co., Ltd.)
Adverse Reaction (Clinically significant adverse reaction)	**Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

2 Antihypertensives

Azilsartan/amlodipine besilate

Brand name	Zacras Combination Tablets LD and HD (Takeda Pharmaceutical Co., Ltd.)
Adverse Reaction (Clinically significant adverse reaction)	**Fulminant hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, etc., or jaundice 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. **Agranulocytosis, leukopenia, and thrombocytopenia:** Agranulocytosis, leukopenia, or thrombocytopenia may occur. Patients should be carefully monitored through clinical laboratory testing, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. **Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

3 **Antihypertensives**

Aliskiren fumarate/amlodipine besilate

Brand name	Rasilamlo Combination Tablets LD and HD (Novartis Pharma K.K.)
Adverse Reaction (Clinically significant adverse reaction)	**Fulminant hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatic function disorder, or jaundice 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. **Agranulocytosis, leukopenia, and thrombocytopenia:** Agranulocytosis, leukopenia or thrombocytopenia may occur. Patients should be carefully monitored through clinical laboratory testing, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. **Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

4 **Antihypertensives**

Irbesartan/amlodipine besilate

Brand name	Aimix Combination Tablets LD and HD (Sumitomo Dainippon Pharma Co., Ltd.)
Adverse Reaction (Clinically significant adverse reaction)	**Fulminant hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, etc. or jaundice 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. **Rhabdomyolysis:** Rhabdomyolysis characterized by myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin may occur. Patients should be carefully monitored. If these symptoms are observed, administration of this drug should be discontinued immediately and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis. **Agranulocytosis, leukopenia, and thrombocytopenia:** Agranulocytosis, leukopenia, or thrombocytopenia may occur. Patients should be carefully monitored through clinical laboratory testing, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

5 **Antihypertensives**

Candesartan cilexetil/amlodipine besilate

Brand name	Unisia Combination Tablets LD and HD (Takeda Pharmaceutical Co., Ltd.), and the others
Adverse Reaction (Clinically significant adverse reaction)	**Fulminant hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, etc. or jaundice 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. **Rhabdomyolysis:** Rhabdomyolysis characterized by myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin may occur. Patients should be carefully monitored. If these symptoms are observed, administration of this drug should be discontinued immediately and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

6 **Antihypertensives**

Telmisartan/amlodipine besilate

Brand name	Micamlo Combination Tablets AP and BP (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse Reaction (Clinically significant adverse reaction)	**Fulminant hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, etc. or jaundice 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. **Rhabdomyolysis:** Rhabdomyolysis characterized by myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin may occur. Patients should be carefully monitored. If these symptoms are observed, administration of this drug should be discontinued immediately and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis. **Agranulocytosis, leukopenia, and thrombocytopenia:** Agranulocytosis, leukopenia, or thrombocytopenia may occur. Patients should be carefully monitored through clinical laboratory testing, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

7 Antihypertensives

Valsartan/amlodipine besilate

Brand name	Exforge Combination Tablets, Exforge Combination OD Tablets (Novartis Pharma K.K.), and the others
Adverse Reaction (Clinically significant adverse reaction)	**Fulminant hepatitis, hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatitis, hepatic function disorder, or jaundice 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. **Rhabdomyolysis:** Rhabdomyolysis characterized by myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin may occur. Patients should be carefully monitored. If these symptoms are observed, administration of this drug should be discontinued immediately and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

8 Miscellaneous cardiovascular agents

Amlodipine besilate/atorvastatin calcium hydrate

Brand name	Caduet Combination Tablets No. 1, No. 2, No. 3, and No. 4 (Pfizer Japan Inc.), and the others
Adverse Reaction (Clinically significant adverse reaction: Amlodipine besilate)	**Fulminant hepatitis, hepatic function disorder, and jaundice:** Fulminant hepatitis, hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT), γ-GTP, etc. or jaundice 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. **Agranulocytosis, leukopenia, and thrombocytopenia:** Agranulocytosis, leukopenia, or thrombocytopenia may occur. Patients should be carefully monitored through clinical laboratory testing, etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted. **Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute kidney injury due to rhabdomyolysis.

9 Miscellaneous metabolism agents

Nintedanib ethanesulfonate

Brand name	Ofev Capsules 100 mg and 150 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Important Precautions	Administration to patients with moderate to severe hepatic function disorder (Child-Pugh B and C) should be avoided unless treatment with this drug is deemed necessary.

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

Tazobactam/piperacillin hydrate

Brand name	Zosyn Intravenous Injections 2.25 g and 4.5 g, Zosyn Intravenous Infusions Bag 4.5 g (Taiho Pharmaceutical Co., Ltd.), and the others
Adverse Reaction (Clinically significant adverse reaction)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and acute generalised exanthematous pustulosis:** Toxic epidermal 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. **Drug-induced hypersensitivity syndrome (DIHS):** Rash and/or pyrexia may occur as initial symptoms, followed by serious late-onset hypersensitivity symptoms with hepatic function disorder, lymphadenopathy, increased white blood cell count, increased eosinophil count, atypical lymphocytes, etc. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be adopted. The reactivation of viruses including Human Herpes Virus 6 (HHV-6) has been frequently found associated with DIHS. Symptoms such as rash, pyrexia, and/or hepatic function disorder may relapse or be prolonged even after discontinuation of administration, and therefore, caution should be exercised.

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

Piperacillin sodium

Brand name	Pentcillin Injections 1 g and 2 g, Pentcillin Injections Bag 1 g and 2 g (Toyama Chemical Co., Ltd.), and the others
Adverse Reaction (Clinically significant adverse reaction)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and acute generalised exanthematous pustulosis:** Toxic epidermal 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.

12 Miscellaneous chemotherapeutics

Atovaquone

Brand name	Samitrel Oral Suspension 15% (GlaxoSmithKline K.K.)
Adverse Reaction (Clinically significant adverse reaction)	**Agranulocytosis and leukopenia:** Agranulocytosis or leukopenia 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.

13 **Antiprotozoans**

Atovaquone/proguanil hydrochloride

Brand name	Malarone Combination Tablets (GlaxoSmithKline K.K.)
Adverse Reaction (Clinically significant adverse reaction)	**Pancytopenia, agranulocytosis, and leukopenia:** Pancytopenia, agranulocytosis, or leukopenia 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

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of December 31, 2015)
◎: Products for which EPPV was initiated after December 1, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Vandetanib Caprelsa Tablets 100 mg	AstraZeneca K.K.	December 24, 2015
◎	Ciprofloxacin Ciproxan Intravenous Infusions 400 mg[*1]	Bayer Yakuhin, Ltd.	December 21, 2015
◎	infliximab (genetical recombination) Remicade Intravenous Infusions 100 mg[*2]	Mitsubishi Tanabe Pharma Corporation	December 21, 2015
◎	Apixaban Eliquis Tablets 2.5 mg, 5 mg[*3]	Bristol-Myers K.K.	December 21, 2015
◎	nivolumab (genetical recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*4]	Ono Pharmaceutical Co., Ltd.	December 17, 2015
◎	leuprorelin acetate Leuplin PRO Injections Kit 22.5 mg	Takeda Pharmaceutical Co., Ltd.	December 15, 2015
◎	absorbed diphtheria-purified pertussis-tetanus-inactivated polio (salk vaccine) combined vaccine Square Kids Subcutaneous Injections Syringe	Kitasato Daiichi Sankyo Vaccine Co., Ltd.	December 9, 2015
◎	venlafaxine hydrochloride Effexor SR Capsules 37.5 mg, 75 mg	Pfizer Japan Inc.	December 8, 2015
◎	Trabectedin Yondelis Intravenous Infusions 0.25 mg, 1 mg	Taiho Pharmaceutical Co., Ltd.	December 7, 2015
◎	Rivaroxaban Xarelto Fine Granules 10 mg, 15 mg[*5]	Bayer Yakuhin, Ltd.	December 7, 2015
◎	None Miticure House Dust Mite Sublingual Tablets 3,300 JAU, 10,000 JAU	Torii Pharmaceutical Co., Ltd.	December 3, 2015
◎	tiotropium bromide hydrate Spiolto Respimat 28 puffs	Nippon Boehringer Ingelheim Co., Ltd.	December 3, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Lusutrombopag Mulpleta Tablets 3 mg	Shionogi & Co., Ltd.	December 1, 2015
◎	Levetiracetam E Keppra Intravenous Infusions 500 mg	UCB Japan Co., Ltd.	December 1, 2015
◎	insulin degludec (genetical recombination) / insulin aspart (genetical recombination) Ryzodeg FlexTouch	Novo Nordisk Pharma Ltd.	December 1, 2015
	sucroferric oxyhydroxide P-TOL Chewable Tablets 250 mg, 500 mg	Kissei Pharmaceutical Co., Ltd.	November 27, 2015
	ombitasvir hydrate/paritaprevir hydrate/ritonavir Viekirax Combination Tablets	AbbVie G.K.	November 26, 2015
	glatiramer acetate Copaxone S.C. Injections 20 mg Syringe	Takeda Pharmaceutical Co., Ltd.	November 26, 2015
	vildagliptin/metformin hydrochloride EquMet Combination Tablets LD and HD	Novartis Pharma K.K.	November 26, 2015
	omarigliptin Marizev Tablets 12.5 mg, 25 mg	MSD K.K.	November 26, 2015
	None Actair House Dust Mite Sublingual Tablets 100 units (IR) and 300 units (IR)	Shionogi & Co., Ltd.	November 19, 2015
	ciprofloxacin Ciproxan Intravenous Infusions 200 mg*6	Bayer Yakuhin, Ltd.	September 24, 2015
	lamotrigine Lamictal Tablets for Pediatric Use 2 mg, 5 mg, Lamictal Tablets 25 mg, 100 mg*7	GlaxoSmithKline K.K.	September 24, 2015
	rivaroxaban Xarelto Tablets 10 mg, 15 mg*8	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*9	Meiji Seika Pharma Co., Ltd.	September 1, 2015

Nonproprietary name Brand name on		Name of the MAH	Date of EPPV initiate
	eliglustat tartrate Cerdelga Capsule 100 mg	Genzyme Japan K.K.	September 1, 2015
	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*10	Air Water Inc.	August 24, 2015
	bosentan hydrate Tracleer Tablets 62.5 mg*11	Actelion Pharmaceuticals Japan Ltd.	August 24, 2015
	ribavirin Rebetol Capsules 200 mg*12	MSD K.K.	July 29, 2015
	clindamycin phosphate hydrate/benzoyl peroxide Duac Combination Gel	GlaxoSmithKline K.K.	July 17, 2015

*1 Pediatric indication and dosage
*2 Acute stage of Kawasaki's disease
*3 Treatment of venous thromboembolism [deep vein thrombosis (DVT) and pulmonary embolism (PE)], and reduction in the risk of recurrent DVT and PE
*4 Unresectable advanced/recurrent non-small cell lung cancer
*5 Treatment of DVT and PE, and reduction in the risk of recurrent DVT and PE
*6 Pediatric indication and dosage
*7 Typical absence seizures
*8 Treatment of DVT and PE, and reduction in the risk of recurrent DVT and PE
*9 Localized, residual recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy
*10 Improvement of pulmonary hypertension in the perioperative period of cardiac surgery
*11 Suppress development of digital ulcers in systemic sclerosis (scleroderma)
*12 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir