Pharmaceuticals and Medical Devices Safety Information

No. 338 November 2016

Table of Contents

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

Available information is listed here

Access to the latest safety information is available via PMDA Medi-navi.

Medi-navi is an email service that provides essential safety information released by the MHLW and PMDA. By registering, you can receive this information on the day of release.

Register here

Published by
Ministry of Health, Labour and Welfare

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

Pharmaceuticals and Medical Devices Safety Information

No. 338 November 2016

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

[Outline of Information]

P: Revision of Precautions *C*: Case Reports

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

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

Abbreviations

ADL	Activities of daily living
ADR	Adverse drug reaction
Afssaps	Agence française de sécurité sanitaire des produits de santé
aHR	Adjusted hazard ratio
ALT	Alanine aminotransferase
aOR	Adjusted odds ratio
APTT	Activated partial thromboplastin time
ARS	Aminoacetyl transfer ribonucleic acid synthetase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBDCA	Carboplatin
CD	Cluster of differentiation
CI	Confidence interval
CK	Creatinine kinase
CNAMTS	Caisse Nationale d'Assurance Maladie des Travailleurs Salaries
CPK	Creatinine phosphokinase
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
E. coli	Escherichia coli
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPPV	Early post-marketing phase vigilance
EU	Europe
Eos	Eosinophils
FDA	Federal Drug Administration
FDP	Fibrin/fibrinogen degradation product
Fib	Fibrinogen
FT3	Free triiodothyronine
FT4	Free thyroxine
FY	Fiscal year
Hb	Hemoglobin
HD	High dose
HMGCR	HMG-CoA reductase
IARC	International Agency for Research on Cancer
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
ITP	Immune thrombocytopenic purpura
IVC	Inferior vena cava
IVIg	Intravenous immunoglobulin
JDIIP	Japan Drug Information Institute in Pregnancy
KL-6	Krebs von den Lunge-6
KPNC	Kaiser Permanente Northern California
LDH	Lactate dehydrogenase
Lym	Lymphocyte
MAH	Manufacturing authorization holder
MB	Myocardial B fraction

MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
NCCHD	National Center for Child Health and Development
Neu	Neutrophils
NHIRD	National Health Insurance Research Database
PaO_2	Arterial oxygen partial pressure
PCPS	Percutaneous cardiopulmonary support
PCR	Polymerase chain reaction
PEM	Pemetrexed
PLT	Platelet
PM	Polymyositis
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PT	Prothrombin time
RBC	Red blood cell
SP-A	Surfactant protein A
SP-D	Surfactant protein D
SRP	Signal recognition particle
TR	Tricuspid regurgitation
TSH	Thyroid stimulating hormone
U.K.	United Kingdom
U.S.	United States
WBC	White blood cell count

1

Interactions in Co-administration of Miconazole and Warfarin Potassium

Active ingredient	(1) Miconazole (2) Warfarin potassium
Brand name (name of company)	(1) Florid Oral Gel 2%, Florid-F for Injection 200 mg (Mochida Pharmaceutical Co., Ltd.) (2) Warfarin Tablets 0.5 mg, 1 mg, 5 mg, Warfarin Granules 0.2% (Eisai Co. Ltd.) and the others
Therapeutic category	(1) Chemotherapeutics-Miscellaneous (2) Anticoagulants
Indications	(1) Florid Oral Gel 2% The following infections associated with genus *Candida*: oral candidiasis, oesophageal candidiasis Florid F for Injection 200 mg The following infections associated with penicillin-suseptible streptococcus pneumoniae among miconazole-sensitive Cryptococcus, Candida, Aspergillus or Coccidioides: Fungaemia, pulmonary mycosis, gastrointestinal mycosis, urinary tract mycosis, and fungal meningitis (2) Treatment and prophylaxis of thromboembolism (including venous thrombosis, myocardial infarction, pulmonary embolism, cerebellar embolism, and slowly progressing cerebral thrombosis)

1. Introduction

Miconazole was approved in 1993 as a gel formulation for the treatment of oral candidiasis and oesophageal candidiasis and in 1985 as an injected drug for the treatment of deep mycosis. The manufacturing authorization holders (MAHs) estimate that miconazole is used by approximately 73 000 patients (gel formulation) and approximately 500 patients (injection formulation) per year (April 2015 to March 2016).

Warfarin potassium (warfarin) was approved in 1962 for the treatment and prophylaxis of thromboembolism, and MAHs estimates that it is used by approximately 1 250 000 patients annually (April 2015 to March 2016).

Recently, given the accumulation of reports of cases of severe bleeding during or after discontinuation of co-administration of miconazole (gel formulation) and warfarin, Ministry of Health, Labour and Welfare (MHLW) has instructed MAHs to revise the precautions. This section presents details of this revision.

2. Occurrences of severe bleeding cases with co-administration of azole antifungals and warfarin

Since the launch of miconazole, there has been a “Precaution for concomitant use” on the package insert for miconazole calling attention to interactions between miconazole and warfarin.

In response to reports of cases of serious bleeding associated with co-administration of miconazole (gel formulation) and warfarin, in 2001, the package insert for miconazole (gel formulation and injection formulation) was revised to instruct “Careful administration” in “patients receiving warfarin” and to add that “miconazole should be co-administered with warfarin carefully,

for example by increasing the frequency of prothrombin time (PT) measurements or thrombotests" to the "Important Precautions" section.

Even after this, reports were made of marked increases in PT-international normalized ratio (INR) in co-administration of these drugs, and cases protracted after co-administration was discontinued were also reported. The package insert was revised in 2014 to add this information to the "Important Precautions" and "Precautions for concomitant use" sections.

However, although the package insert was revised to call greater attention to this drug interaction, serious cases of bleeding in co-administration of these drugs continue to be reported. A survey by the Pharmaceuticals and Medical Devices Agency (PMDA) found that since 2013, there have been many reports of cases where it was not possible to control PT-INR by reducing the dose of warfarin, leading to warfarin being discontinued, or cases where PT-INR continued to increase even after co-administration was ended, and there have also been reports of cases where, even though the physician was careful about concomitant use and took care to check PT-INR frequently, it was still not possible to prevent serious bleeding due to a drug interaction. Therefore, we consider that it is not feasible to avoid this risk by further enhancing measures such as monitoring of the anticoagulant effect. On October 18, 2016, MHLW instructed the MAHs of miconazole and warfarin to revise the precautions on use to contraindicate co-administration of miconazole (gel formulation and injection formulation) and warfarin. Moreover, MHLW issued a notification by the director of the Safety Division (SD) (Notification of Pharmaceutical Safety and Environmental Health Bureau No. 1018-4, dated October 18, 2016) to relevant academic societies such as the Japanese Circulation Society and the Japanese Society of Chemotherapy to request dissemination of the measure adopted.

Regarding other oral and injection azole antifungals than miconazole (*i.e.* itraconazole, fluconazole, fosfluconazole, and voriconazole), considering the marked PT-INR elevation in albeit limited number of adverse drug reaction (ADR) reports in proportion to the number of patients using them as estimated by MAHs, MHLW has instructed to specify "patients receiving warfarin" in "Careful administration" and add that "care should be taken when co-administering with warfarin, for example by increasing the frequency of PT measurements or thrombotests" to the "Important Precautions" section.

3. Cases relating to bleeding due to interaction between minaconazole and warfarin

PMDA has been reported on events related to bleeding in co-administration of miconazole and warfarin in 41 cases (including one fatal case*) for the past 3 years (from April 2013 to July 2016) including those with causal relationship unknown. The clinical courses of two cases relating to bleeding due to interaction between miconazole and warfarin are presented below.

Case 1

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
1	Female 80s	Oral candidiasis (atrial fibrillation, asthma, dyslipidaemia, chronic cardiac failure, angina pectoris)	20 g 7 days	**Lower gastrointestinal haemorrhage, INR increased, drug interaction** Approximately 4 years before administration Administration of warfarin potassium at 3 mg/day was started as treatment for atrial fibrillation. Day 1 of administration PT-INR before administration of miconazole: 2.59. Administration of miconazole for oral candidiasis was started at a dose of 5 g 4 times per day. Day 7 of administration (day of discontinuation) Miconazole was discontinued. 10 days after discontinuation Since 2 days earlier, black stools had been observed, and the patient made an outpatient visit to the reporting medical institution. PT-INR had increased above the

				upper limit of quantitation (estimated PT-INR>20). From a computed tomography (CT) scan and digital rectal examination, gastrointestinal haemorrhage was strongly suspected, and the patient was admitted as an emergency case. Menatetrenone 20 mg was administered by intravenous injection. PT-INR: 8.68. Warfarin potassium was discontinued. Red cell concentrate-leukocyte reduced (4 units) was administered. The patient was fully conscious and complained only of a feeling of discomfort. 13 days after discontinuation PT-INR 3.54. Menatetrenone 10 mg was administered by intravenous injection. PT-INR 1.62. Endoscopy of the upper gastrointestinal tract was performed. Bleeding of the upper gastrointestinal tract was absent. Endoscopy of the lower gastrointestinal tract was performed. Active bleeding was absent, but redness was present, and diverticular bleeding was diagnosed. 17 days after discontinuation PT-INR 3.06. Menatetrenone 10 mg was administered by intravenous injection. PT-INR 1.80. 24 days after discontinuation Administration of apixaban was started for atrial fibrillation. 30 days after discontinuation PT-INR 1.41. As symptoms had been resolving, the patient was discharged.
	Suspected concomitant drug: warfarin potassium Concomitant medications: verapamil hydrochloride, atorvastatin calcium hydrate, montelukast sodium, fudosteine, rebamipide, prednisolone, budesonide/formoterol fumarate hydrate, ambroxol hydrochloride, sodium rabeprazole, magnesium oxide, furosemide			

*Case that claimed relief benefits under the ADR Relief System

Laboratory examination

	Before start of administration	10 days after discontinuation		11 days after discontinuation	12 days after discontinuation	13 days after discontinuation	
		At outpatient examination	After treatment			At examination	After treatment
Hb (g/dL)	13.8	8.7	7.7	8.0	6.9	9.2	–
PT-INR	2.59	Estimate >20	8.68	1.18	1.79	3.54	1.62

	14 days after discontinuation	17 days after discontinuation		18 days after discontinuation	21 days after discontinuation	24 days after discontinuation	30 days after discontinuation
		At examination	After treatment				
Hb (g/dL)	9.0	9.1	–	9.9	9.6	9.2	10.3
PT-INR	1.10	3.06	1.80	3.54	1.78	1.56	1.41

Case 2

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
2	Female 50s	Oral candidiasis (antiphospholipid syndrome, systemic lupus erythematosus, asthma)	20 g 7 days	**INR increased, drug interaction, abdominal pain, back pain** Approximately 3 years before administration Warfarin potassium was prescribed at 2.5 mg once per day to treat antiphospholipid syndrome. 15 days before administration PT-INR: 2.15.

				Day 1 of administration Administration of miconazole at 20 g/day was started for oral candidiasis. Day 7 of administration (day of discontinuation) Administration of miconazole was discontinued. 7 days after discontinuation Abdominal pain and back pain were present. At an examination, PT-INR was >10. The patient was admitted as an emergency case. At admission, there were no subjective symptoms such as oral or bleeding in the lower limb. After admission, menatetrenone 10mg × 2 was administered. Warfarin potassium was discontinued. The course of back pain was observed, and after discharge, back pain was resolving. 8 days after discontinuation PT-INR: 1.44. Warfarin potassium was resumed at a reduced dose of 1 mg. 10 days after discontinuation The patient was discharged. 21 days after discontinuation PT-INR: 3.13. Warfarin potassium was continued at 1 mg. 49 days after discontinuation The patient recovered.
	Suspected concomitant drug: warfarin potassium Concomitant medications: prednisolone, alfacalcidol, famotidine, fexofenadine hydrochloride, rosuvastatin calcium, ezetimibe			

Laboratory examination

	15 days before administration	7 days after discontinuation	8 days after discontinuation	10 days after discontinuation	21 days after discontinuation	49 days after discontinuation
PT-INR	2.15	>10	1.44	2.75	3.13	1.23

4. Precaution about co-administration of warfarin with azole antifungals

Healthcare professionals should pay attention to the following issues.

(1) Before prescribing miconazole and other azole antifungals, check in advance whether the patient is taking warfarin.

(2) If the patient is taking warfarin, give priority to treatment with warfarin, and do not prescribe miconazole.

(3) When administering an azole antifungal agent other than miconazole to a patient taking warfarin, enhance monitoring of blood coagulation ability, for example by increasing the number of measurements of PT and thrombotests. Monitor the patient, being careful about bleeding-related adverse reactions, and also instruct the patient to contact his or her physician immediately if a bleeding-related adverse reaction is suspected.

(4) When administering an azole antifungal to a patient taking warfarin, caution should be exercised, for example by keeping in contact with a specialist in circulatory medicine or the physician prescribing warfarin.

5. Closing comments

Refer to p. 39 “5. Revision of Precautions” in this issue, which provides the current revision of the package insert.

Overseas, co-administration of miconazole and warfarin is contraindicated in France, and in the United Kingdom (U.K.) in 2016, in response to reports of adverse reactions suspected to be interactions between miconazole and warfarin, including deaths due to bleeding events, the Medical and Healthcare products Regulatory Agency again called attention to this drug interaction and announced that it was considering taking additional measures[1)].

<References>

1) Drug Safety Update (Medicines and Healthcare products Regulatory Agency) https://www.gov.uk/drug-safety-update/topical-miconazole-including-oral-gel-reminder-of-potential-for-serious-interactions-with-warfarin

<Reference Information>

The number of patients using azole antifungals other than miconazole in the past one year estimated by MAHs.

Itorazonazole	590 000
Fluconazole	860 000
Fosfluconazole	10 000
Voriconazole	25 000

2

Safety Measures against Bladder Cancer Associated with Diabetes Medication "Pioglitazone Hydrochloride-Containing Products"

Active ingredient	(1) Pioglitazone hydrochloride (2) Pioglitazone hydrochloride/metformin hydrochloride (3) Pioglitazone hydrochloride/glimepiride (4) Pioglitazone hydrochloride/alogliptin benzoate
Brand name (name of company)	(1) Actos Tablets 15 mg, 30 mg, Actos OD Tablets 15 mg, 30 mg (Takeda Pharmaceutical Company Limited) (2) Metact Combination Tablets LD & HD (Takeda Pharmaceutical Company Limited) (3) Sonias Combination Tablets LD & HD (Takeda Pharmaceutical Company Limited) (4) Liovel Combination Tablets LD & HD (Takeda Pharmaceutical Company Limited)
Therapeutic category	Antidiabetic agents
Indications	(1) Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments and may have insulin resistance: 1) a. Diet and exercise therapies alone b. Sulfonylurea along with diet and exercise therapies c. α-glucosidase inhibitor along with diet and exercise therapies d. Biguanide along with diet and exercise therapies 2) Insulin along with diet and exercise therapies (2) Type 2 diabetes mellitus To be used only when the concomitant use of pioglitazone hydrochloride and metformin hydrochloride is considered appropriate. (3) Type 2 diabetes mellitus To be used only when the concomitant use of pioglitazone hydrochloride and glimepiride is considered appropriate. (4) Type 2 diabetes mellitus To be used only when the concomitant use of alogliptin benzoate and pioglitazone hydrochloride is considered appropriate.

1. Introduction

Pioglitazone hydrochloride (hereinafter referred to as "pioglitazone") is an antidiabetic agent used to lower blood glucose by reducing insulin resistance, inhibiting glucose production in the liver, and promoting sugar utilization in the peripheral tissue. In Japan, pioglitazone alone was approved in September 1999, and 3 combination drugs have been approved since then until now.

Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 283 (reference 1) introduced safety measures against bladder cancer for pioglitazone. The current issue now introduces the updated information based on the latest results of investigations conducted by PMDA.

2. Background and past investigations relating to bladder cancer risk

The investigations and response by MHLW and PMDA based on the measures taken in other countries regarding the bladder cancer risk of pioglitazone and the information obtained are as follows.

Time	Country taking measures	Measures
June 9, 2011	France	The French regulatory authority (Agence française de sécurité sanitaire des produits de santé [Afssaps]) issued a notification to suspend new prescriptions of pioglitazone based on an epidemiological study (Caisse Nationale d' Assurance Maladie des Travailleurs Salaries [CNAMTS] study) that reported a possible risk of bladder cancer in patients treated with pioglitazone
June 10, 2011	Germany	The German regulatory authority issued a similar restriction on use
June 15, 2011	United States (U.S.)	The U.S. Federal Drug Administration (FDA) issued a Drug Safety Communication that pioglitazone should not be used for active bladder cancer, based on the 5-year interim analysis of a 10-year observational cohort study (the Kaiser Permanente Northern California [KPNC] research) in patients with diabetes mellitus in the U.S.
June 23, 2011	Japan	Discussed at the Second 2011 Subcommittee on Drug Safety of the Committee on Drug Safety (reference 2)
	Europe (EU)	The European Medicines Agency (EMA) did not suspend the use of pioglitazone and announced that it would review this matter based on EU-wide discussions to determine appropriate actions
June 24, 2011	Japan	Instructions given to revise the Important Precautions and Other Precautions on the package insert
July 29, 2011	Japan	The series of responses in Japan from June 23, 2011, onwards were reported at the First 2013 Subcommittee on Drug Safety of the Committee on Drug Safety (reference 3)

The revision of precautions on June 24, 2011 alerted healthcare professionals as follows based on epidemiological studies conducted overseas in patients with diabetes mellitus;

- administration should be avoided in patients with active bladder cancer
- administration should be carefully considered in patients with history of bladder cancer
- patients and their families should be informed of the risk of bladder cancer prior to the start of administration
- periodic urine tests should be performed during administration

Recently, the final results of the KPNC epidemiological study have been obtained at Year 10, and, therefore, PMDA has reviewed the bladder cancer risk in patients treated with pioglitazone again including consideration of the results of this study.

3. Results of investigations for bladder cancer risk

(1) Outline of epidemiological and other studies

Since July 2011, 51 epidemiological studies on the onset of bladder cancer have been reported to PMDA excluding duplications. Of these, major studies are outlined below.

1) KPNC epidemiological study (published article: JAMA, 314(3): 265, 2015) (reference 4)

The KPNC study was conducted as manufacturer-sponsored at the University of Pennsylvania. Between January 1997 and December 2002, the study investigated the relationship between pioglitazone and the occurrence of bladder cancer based on data in 193 099 patients with diabetes aged 40 and above who were members of the KPNC health plan (34 181 patients treated with pioglitazone and 158 918 patients not treated with pioglitazone). Patients were followed up

until December 2012.

The hazard ratio adjusted for potential confounding factors (adjusted hazard ratio; aHR) for the risk of bladder cancer in patients treated with pioglitazone relative to patients not treated with pioglitazone was 1.06 [95% confidence interval (CI), 0.89 - 1.26], and therefore a statistically significant increase in risk was not found. Data was stratified by the time since administration of pioglitazone was started, by cumulative exposure period, and by cumulative dose, but no statistically significant increase in risk was found for any strata (Table 1).

In a nested case control study using the same cohort, the result for the adjusted odds ratio (aOR) for the occurrence of bladder cancer with pioglitazone was similar to that for the cohort study, and no statistically significant increase in risk was shown (aOR 1.18 [95% CI, 0.78 - 1.80]).

In the 5-year interim analysis, a statistically significant increase in bladder cancer risk was observed in the stratum for a ≥2 years cumulative exposure period, and therefore the final 10-year analysis data was stratified using the same categories as for the 5-year interim analysis, with the result that no statistically significant increase in the risk of bladder cancer was found in the stratum for a ≥2 years cumulative exposure period (aHR 1.09 [95% CI, 0.88 - 1.36]), but when the stratum for a ≥2 years period was categorized further, the stratum for a ≥4.1 years period and <6 years period had the highest risk of bladder cancer, although it was not statistically significant (aHR 1.29 [95% CI, 0.91 - 1.82]). Additionally, while the stratum for a 40 000 mg cumulative dose did not show any statistically significant increase in bladder cancer risk (aHR 1.07 [95% CI, 0.79 - 1.44]), a statistically significant increase in bladder cancer risk was also found for the stratum with a cumulative dose ≥28 001 mg and <40 000 mg (aHR 1.53 [95% CI, 1.07 - 2.18]) (Table 2).

The University of Pennsylvania remarked that possible factors responsible for the discrepancy between the results of 5-year interim analysis and final 10-year analysis include the biological characteristics of tumor promoters, detection bias, changes in prescription patterns or bladder cancer screening, and coincidence, but that no factor can explain all of the results observed, and additional follow-up studies that can be compared with this study are necessary.

Table 1 Results of Final Analysis of the KPNC Study[1)]

			Number of patients with bladder cancer	Observed person-years	Incidence rate of bladder cancer (per 100,000 person-years) (95% CI)		Adjusted HR [2)] (95% CI)	
Overall	Administration of pioglitazone	Patients not treated with pioglitazone	1075	1 417 196	75.9	(71.3-80.4)	1 [control]	
		Patients treated with pioglitazone	186	207 112	89.8	(76.9-102.7)	1.06	(0.89-1.26)
Stratified analysis	Time since administration of pioglitazone was started (years)	<4.5	88	129 017	68.2	(54.0-82.5)	0.89	(0.71-1.12)
		4.5-8.0	65	58 247	111.6	(84.5-138.7)	1.21	(0.93-1.59)
		>8.0	33	26 234	125.8	(82.9-168.7)	1.2	(0.83-1.75)
	Cumulative exposure period (years)	<1.5	60	88 839	67.5	(50.4-84.6)	0.88	(0.68-1.16)
		1.5-4.0	69	78 059	88.4	(67.5-109.3)	1.03	(0.80-1.33)
		>4.0	57	50 145	113.7	(84.2-143.2)	1.16	(0.87-1.54)
	Cumulative dose (mg)	1-14 000	66	95 534	69.1	(52.4-85.8)	0.9	(0.69-1.16)
		14 001-40 000	69	71 198	96.9	(74.0-119.8)	1.1	(0.85-1.42)
		>40 000	51	50 310	101.4	(73.5-129.2)	1.07	(0.79-1.44)

Notes

1) Excerpted from Table 2. Crude Incidence Rate and Hazard Ratios for the Association Between Pioglitazone Use and Risk of Bladder Cancer Among 193 099 Persons
2) The statistical model includes all surveyed potential confounding factors, including proteinuria tests.

Table 2 Post-Hoc Analysis Results of KPNC Final Analysis Data Stratified Using the Same Categories as 5-Year Interim Analysis

				Number of patients with bladder cancer	Observed person-years	Adjusted HR[4] (95% CI)
Overall [5]	Patients not treated with/treated with pioglitazone[5]	Patients not treated with pioglitazone		1075	1 417 196	1 [control]
		Patients treated with pioglitazone		186	207 112	1.06 (0.89 - 1.26)
Stratified analysis [3]	Time since administration of pioglitazone was started (years)	< 1.5		34	49 135	0.98 (0.69 - 1.38)
		1.5-3.0		27	43 246	0.81 (0.55 - 1.20)
		> 3.0		125	121 190	1.12 (0.91 - 1.38)
			3.1-4.4	27	36 709	0.88 (0.60 - 1.31)
			4.5-8	65	58 247	1.21 (0.93 - 1.59)
			> 8	33	26 234	1.20 (0.83 - 1.75)
	Cumulative exposure period (years)	< 1		39	62 577	0.83 (0.60 - 1.15)
		1.0-2.0		40	47 568	1.06 (0.77 - 1.46)
		> 2.0		107	107 011	1.09 (0.88 - 1.36)
			2.1-4	50	56 866	1.01 (0.75 - 1.35)
			4.1-6	36	29 558	1.29 (0.91 - 1.82)
			> 6	21	20 587	0.99 (0.63 - 1.55)
	Cumulative dose (mg)	1-10 500		55	78 693	0.92 (0.70 - 1.22)
		10 501-28 000		47	63 919	0.87 (0.64 - 1.18)
		> 28 000		84	74 431	1.23 (0.96 - 1.56)
			28 001-40 000	33	24 121	1.53 (1.07 - 2.18)
			> 40 000	51	50 310	1.07 (0.79 - 1.44)

Notes

3) Excerpted from eTable 4. Analysis of Bladder Cancer Risk and Duration of Exposure to Pioglitazone with Alternative Categories of Exposure Including the Categories Used in the Prior Report of this Cohort among 193,099 Patients: Kaiser Permanente Northern California Diabetes Registry

4) The statistical model includes all surveyed potential confounding factors, including proteinuria tests.

5) Excerpted from Table 2. Crude Incidence Rate and Hazard Ratios for the Association Between Pioglitazone Use and Risk of Bladder Cancer Among 193 099 Persons

2) Pan EU study (published article: BMJ, 354: i3909, 2016) (reference 5)

EPID Research conducted a non-interventional, register-based linkage cohort study in patients with type 2 diabetes mellitus, using 6 databases in 4 countries (Finland, the Netherlands, Sweden, and the U.K.) as the MAH's sponsored research. Using 1:1 matching by propensity score, 56 337 patients treated with pioglitazone and the same number of patients not treated with pioglitazone were identified and used as the analysis set. Of the 283 patients diagnosed with bladder cancer during the observation period, 130 were patients treated with pioglitazone and 153 were patients not treated with pioglitazone., No increase in bladder cancer risk associated with pioglitazone was found (aHR 0.99 [95% CI, 0.75 - 1.30]), and stratified analysis for cumulative exposure period and cumulative dose also found no association between pioglitazone and increased bladder cancer risk.

3) PROactive study (published article: Diabetes Obes Metab. 2015 Nov 23) (reference 6)

The MAH conducted a 10-year European multi-center observational study in patients participating in the PROactive study. After administration of pioglitazone or placebo under double-blind conditions in the PROactive study (observation period: 3 years), patients shifted to a follow-up surveillance period. Data from routine clinic visits were followed up every 2 years, and any death, morbidity rate of macroangiopathy, and occurrences of malignant tumor were assessed. In both periods, the PROactive study (a double-blind period) and the observational study (a follow-up surveillance period), the ratio of patients who developed bladder cancer by group in the double-blind period were 1.0% (27/2,605 patients) in the pioglitazone group and 1.0% (26/2,633 patients) in the placebo group. The Risk Ratio (RR) was 1.05 [95% CI, 0.61 - 1.79], and thus no statistically significant increase in bladder cancer risk was found.

4) Epidemiological study using the U.K. General Practice Research Database (published article: BMJ, 344: e3645, 2012) (reference 7)

The Jewish General Hospital conducted a cohort study in 115 727 patients with type 2 diabetes mellitus in the U.K. General Practice Research Database who were newly administered diabetes drugs from January 1988 to December 2009. As a result, during the follow-up period (mean follow-up period: 4.6 years), 470 patients were diagnosed with bladder cancer (89.4/100,000 person-years).

Using the same cohort, a nested case control study was performed, with the analysis set consisting of 376 patients newly diagnosed with bladder cancer ≥1 year after the start of follow-up (cases) who were matched by age, cohort entry date, sex, and duration of follow-up with 6 699 patients without bladder cancer (controls). When the relative risk was calculated, a statistically significant increase in bladder cancer risk was found in patients treated with pioglitazone compared with patients not treated with pioglitazone (adjusted Rate ratio: 1.83 [95% CI, 1.10 - 3.05]). Statistically significant increases in bladder cancer risk were also found in the stratum of patients with a ≥24 months time since administration of pioglitazone was started (adjusted Rate ratio: 1.99 [95% CI, 1.14 - 3.45]) and the stratum of patients with a cumulative dose >28 000 mg (adjusted Rate ratio: 2.54 [95% CI, 1.05 - 6.14]).

5) Epidemiological research using the Taiwan National Health Insurance Research Database (published article: Drug safety 36(8): 643, 2013) (reference 8)

National Taiwan University conducted a nested case control study using an analysis set consisting of 3 412 patients with bladder cancer (cases), matched 1:5 by age, sex, and enrollment date to 17 060 patients without bladder cancer (controls) among the outpatients who were diagnosed with type 2 diabetes mellitus from 1997 to 2008 according to the National Health Insurance research database (NHIRD).

In current users of pioglitazone (patients for whom the prescription period of pioglitazone included the date of initial admission for bladder cancer or for whom the final date of the prescription period of pioglitazone was within 90 days prior to the date of initial admission), a statistically significant relationship with bladder cancer risk was found (aOR: 2.39 [95% CI, 1.75 - 3.25, $p < 0.01$]). The bladder cancer risk tended to be higher as the cumulative administration period of pioglitazone became longer: for the stratum with a cumulative administration period <1 year, aOR was 1.45 [95% CI, 1.12 - 1.87, $p < 0.01$], for the stratum with a cumulative administration period ≥1 year and <2 years, aOR was 1.74 [95% CI, 1.05 - 2.90, $p = 0.03$], and for the stratum with a cumulative administration period ≥2 years, aOR was 2.93 [95% CI, 1.59 - 5.38, $p < 0.01$].

(2) Adverse reactions in Japan

Up to 31 May 2016, the adverse reactions in Japan relating to bladder cancer reported to PMDA for formulations containing pioglitazone are 333 occurrences of “bladder cancer,” 89 occurrences of “bladder transitional cell carcinoma,” 22 occurrences of “bladder neoplasm,” 12 occurrences of “recurrent bladder cancer,” 7 occurrences of “bladder cancer stage 0, with cancer in situ,” 7 occurrences of “transitional cell carcinoma,” and 1 occurrence each of “bladder squamous cell carcinoma,” “bladder papilloma,” and “benign neoplasm of bladder.”

(3) Responses overseas

In July 2015, the MAH revised the Company Core Safety Information in view of the final results of the KPNC study and the results of the Pan EU study, and a draft revision of the package insert with the same content was submitted to the EMA and FDA. In April 2016, revision of the package inserts of formulations containing pioglitazone was recommended in Europe, and in June 2016, the "Special warning and precautions for use" section was revised. As of June 2016, this matter is under consideration at the FDA, and as of the end of June 2016, no other countries have taken new measures in response to the final results of the KPNC study.

(4) Evaluation of the International Agency for Research on Cancer (IARC)

In June 2013, as a result of evaluation based on the results published so far, it was concluded that regarding pioglitazone, "there is sufficient evidence about carcinogenicity in test animals, but insufficient evidence about carcinogenicity in humans. The overall assessment is that it is probably carcinogenic in humans." and it has been classified into IARC carcinogenicity category 2A (probably carcinogenic in humans).

4. Results of investigation and safety measures

Regarding the recently obtained final results of the KPNC study, PMDA considers that, at present, it is difficult to make an adequate interpretation about the causal factors leading to the discrepancy between the results of 5-year interim analysis and final 10-year analysis in the KPNC epidemiological study. However, as a result of detailed investigation of related reports, responses in Japan and overseas, and other information received between July 2011 and May 31, 2016, PMDA have determined that the possibility of an increase in bladder cancer risk caused by pioglitazone cannot be excluded.

5. Future safety measures

A draft revision of the package inserts for formulations containing pioglitazone has been submitted by the MAH, and it has been explained that it is appropriate to provide information on the latest results relating to pioglitazone and bladder cancer risk, including the KPNC epidemiological study and Pan EU study in the "Other Precautions" section and to continue to call attention to the risk in the "Important Precautions" section.

MHLW, based on the discussion and decision by PMDA, has determined that it is appropriate to revise the package inserts according to the following policy.

- As the possibility that pioglitazone increases bladder cancer risk cannot be excluded, the "Important Precautions" section should continue to call attention to this risk.
- In the "Other Precautions" section, the current statement about the results of 5-year interim analysis in the KPNC study and the results of the CNAMTS study should be deleted, and an addition should be made to state that in 10-year large-scale cohort studies (the final results of the KPNC epidemiological study and the Pan EU study), a statistically significant difference in bladder cancer risk was not found. On the other hand, as several epidemiological studies including the KPNC study have suggested that there is a possibility of increased bladder cancer risk, this fact should be stated.

We will continue to pay attention to new reports on epidemiological research and measures taken by overseas regulatory authorities in the future, and consider taking necessary actions.

6. References

(1) Safety Measures against Bladder Cancer Associated with Diabetes Medication "Pioglitazone Hydrochloride-Containing Products" (PMDSI No. 283)
https://www.pmda.go.jp/files/000153428.pdf

(2) Safety Measures Associated with Pioglitazone Hydrochloride-Containing Products (June 23, 2011: Materials for the Second 2013 Subcommittee on Drug Safety of the Committee on Drug Safety)
http://www.mhlw.go.jp/stf/shingi/2r9852000001hbq8.html (only available in Japanese language)

(3) Safety Measures Associated with Pioglitazone Hydrochloride-Containing Products (July 29, 2011: Materials for the First 2013 Subcommittee on Drug Safety of the Committee on Drug Safety)
http://www.mhlw.go.jp/stf/shingi/2r9852000001le8l.html (only available in Japanese language)

(4) KPNC Epidemiological Study
Lewis JD et al. Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons with Diabetes. (JAMA, 314(3): 265, 2015)

(5) Pan EU Study
Korhonen P. et al. Pioglitazone Use and Risk of Bladder Cancer in Patients with Type 2 Diabetes: Retrospective Cohort Study Using Datasets from Four European Countries（BMJ, 354: i3903, 2016）

(6) PROactive Study: 10-year observational study
Erdmann E et al. 10-Year Observational Follow-Up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. (Diabetes Obes Metab. 2015 Nov 23.)

(7) Study using the U.K. General Practice Research Database
Azoulay L et al. The use of pioglitazone and risk of bladder cancer in people with type 2 diabetes: nested case-control study. (BMJ, 344: e3645, 2012)

(8) Study using the Taiwan NHIRD
Hsiao FY et al. Risk of Bladder Cancer in Diabetic Patients Treated with Rosiglitazone or Pioglitazone: A Nested Case-Control Study. (Drug safety, 36(8): 643, 2013)

3

Project of the Japan Drug Information Institute in Pregnancy

1. Project 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 (NCCHD) in October 2005 to provide consultation services to pregnant women and women who wish to become pregnant based on the latest scientific evidence. The JDIIP also evaluates pregnancy outcome in consultation clients to establish new evidence. It has been introduced in PMDSI No. 328, etc.

2. Cooperating medical institutions

The system for consultation services and prompt information collection of the JDIIP was strengthened in fiscal year (FY) 2015, by receiving the cooperation of 5 hospitals (Yamagata University Hospital, University of Fukui Hospital, Shimane University Hospital, Saga University Hospital, and Nagasaki University Hospital) newly joined, in order to enhance the accessibility. The cooperating hospitals are introduced below. (Page 20).

3. To 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. Patients who have received consultation services from the JDIIP or cooperating medical institutions have told us that it relieved their concerns about taking drugs.

- Consultation services and procedure:
  http://www.ncchd.go.jp/en/center/activity/JDIIP/index.html

4. New initiatives of the JDIIP

The JDIIP receives over 2 000 consultations per year, and while the accumulation of information is proceeding smoothly, information on drug package inserts relating to use in pregnant women and nursing mothers is not always adequate. Therefore, this year, an initiative has started to assist in organizing and evaluating the information accumulated by the JDIIP and updating the information on package inserts about using in pregnant women and nursing mothers to reflect the effort.

The specific procedure is as follows: First, the JDIIP considers the consultations it has received up to the present, selects drugs for which necessity for revision of package inserts is considered high, and works in collaboration with pharmaceutical manufacturers in Japan to gather a broad range of information about the selected drugs, including their usage in Japan, package inserts in Japan and overseas, guidelines, textbooks, content of specialist databases, details of animal tests and basic studies, and published literature articles in Japan and overseas. JDIIP then uses this information to prepare materials for consideration, and then these are evaluated and considered by a working group including JDIIP staff (obstetric medicine specialists and pharmacists) and also obstetricians, pediatricians, pharmacists, specialists in animal testing, etc. The information considered by the working group is provided to government organizations and related companies as a report, and revision of the package insert is considered.

At present, information about tacrolimus, azathioprine, and ciclosporin is being collected.

List of cooperating medical institutions for FY 2016

	Name of medical institution	Contact information, reception hours, etc.
1	Japan Drug Information Institute in Pregnancy	Address: 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 in 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) http://www.ncchd.go.jp/en/center/activity/JDIIP/index.html
Cooperating hospitals (◎: Joined in 2016)		
2	Hokkaido University Hospital	Address: 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 – 16:00 (Monday to Friday, excluding national holidays)
3	Hirosaki University Hospital	Address: 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	Address: 19-1 Uchimaru, Morioka-city, Iwate 020-8505 TEL: (+81)-19-624-5263 (Pregnancy and drugs counseling desk: Direct call) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
5	◎ Yamagata University Hospital	Address: 2-2-2, Iida-nishi, Yamagata-city, Yamagata 990-9585 TEL: (+81)-23-633-1122 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 8:30 –17:00 (Monday to Friday, excluding national holidays)
6	Tohoku University Hospital	Address: 1-1 Seiryo-machi, Aoba-ku, Sendai-city, Miyagi 980-8574 TEL: (+81)-22-717-7000 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) HP: http://www.hosp.tohoku.ac.jp/ (only available in Japanese language)
7	Fukushima Medical University Hospital	Address: 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/univ/en/
8	Tsukuba University Hospital	Address: 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)
9	Maebashi Red Cross Hospital	Address: 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) HP: http://www.maebashi.jrc.or.jp/ (only available in Japanese language)

10	Saitama Medical University Hospital	Address: 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)
11	Chiba University Hospital	Address: 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)
12	Toranomon Hospital	Address: 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)
13	St. Luke’s International Hospital	Address: 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)
14	Yokohama City University Hospital	Address: 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) HP: http://www.fukuhp.yokohama-cu.ac.jp/ (only available in Japanese language)
15	Niigata University Medical & Dental Hospital	Address: 1-754 Asahimachi-dori, Chuo-ku, Niigata-city, Niigata 951-8520 TEL: (+81)-25-227-2793 (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)
16	Shinshu University Hospital	Address: 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)
17	University of Toyama Hospital	Address: 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)
18	National Hospital Organization Kanazawa Medical Center	Address: 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) HP: http://www.kanazawa-hosp.jp/pv/preg.htm (only available in Japanese language)
19	◎ University of Fukui Hospital	Address: 23-3, Matsuoka-shimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193 TEL: (+81)-776-61-3111 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 13:00 – 15:00 (Monday to Friday, excluding national holidays)

20	Hamamatsu University Hospital	Address: 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 year-end/new-year) HP: https://www.hama-med.ac.jp/hos/hospital-e.html
21	National Hospital Organization Nagara Medical Center	Address: 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)
22	Japanese Red Cross Nagoya Daiichi Hospital	Address: 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)
23	Mie University Hospital	Address: 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)
24	University Hospital, Kyoto Prefectural University of Medicine	Address: 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)
25	Osaka Medical Center and Research Institute for Maternal and Child Health	Address: 840 Murodo-cho, Izumi-city, Osaka 594-1101 TEL: (+81)-725-56-5537 (Outpatient service for pregnancy and drugs) Reception hours: 10:00 – 12:00, 14:00 – 17:00 (Monday to Friday, excluding national holidays) HP: http://www.mch.pref.osaka.jp/english/index.html
26	Kobe University Hospital	Address: 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)
27	Nara Medical University Hospital	Address: 840 Shijo-cho, Kashihara-city, Nara 634-8522 TEL: (+81)-744-22-3051 (Division of Pharmacy: Extension 3567) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) HP: http://www.naramed-u.ac.jp/hospital/shinryoka-bumon/senmongairai/ninshintokusuri.html (only available in Japanese language)
28	Japanese Red Cross Wakayama Medical Center	Address: 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) HP: http://www2.kankyo.ne.jp/nisseki-w/others/en.html

29	Tottori University Hospital	Address: 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) HP: http://www2.hosp.med.tottori-u.ac.jp/en/
30	National Hospital Organization Okayama Medical Center	Address: 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) HP: http://okayamamc.jp/04_bumon/04-04_bumon/04-04_03-02yakuzai.html (only available in Japanese language)
31	◎ Shimane University Hospital	Address: 89-1, Enya-cho, Izumo-city, Shimane 693-8501 TEL: (+81)-853-20-2061 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)
32	Hiroshima University Hospital	Address: 1-2-3 Kasumi, Minami-ku, Hiroshima-city, Hiroshima 734-8551 TEL: (+81)-82-257-5064 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
33	National Hospital Organization Shikoku Medical Center for Children and Adults	Address: 2-1-1 Senyu-cho, Zentsuji-city, Kagawa 765-8507 TEL: (+81)-877-62-1000 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-877-62-6311 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
34	Tokushima University Hospital	Address: 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)
35	Kyushu University Hospital	Address: 3-1-1 Maidashi, Higashi-ku, Fukuoka-city, Fukuoka 812-8582 TEL: (+81)-92-642-5900 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 14:00 – 17:00 (Monday to Friday, excluding national holidays)
36	◎ Saga University Hospital	Address: 5-1-1 Nabeshima, Saga-city, Saga 849-8501 TEL: (+81)-952-34-3482 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
37	Japanese Red Cross Kumamoto Hospital	Address: 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)

38	University of Miyazaki Hospital	Address: 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) HP: http://www.med.miyazaki-u.ac.jp/home/hospital/for-foreigners/
39	◎ Nagasaki University Hospital	Address: 1-7-1, Sakamoto, Nagasaki-city, Nagasaki 852-8501 TEL: (+81)-95-819-7249 Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays)
40	Kagoshima City Hospital	Address: 37-1, Uearata-cho, Kagoshima-city, Kagoshima 890-8760 TEL: (+81)-99-230-7000 (Pharmacy department: Extension 2271) (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-99-230-7075 Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)
41	Okinawa Chubu Hospital	Address: 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)

<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
- PMDSI No. 328: https://www.pmda.go.jp/files/000208994.pdf

4

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated October 18, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 (a) Atorvastatin calcium hydrate
(b) Simvastatin
(c) Pitavastatin calcium hydrate
(d) Pravastatin sodium
(e) Fluvastatin sodium
(f) Rosuvastatin calcium

Brand name (name of company)	(a) Lipitor Tablets 5 mg, 10 mg (Astellas Pharma Inc.), and the others (b) Lipovas Tablets 5 mg, 10 mg, 20 mg (MSD K.K.), and the others (c) Livalo Tab. 1 mg, 2 mg, 4 mg, Livalo OD Tab. 1 mg, 2 mg, 4 mg (Kowa Company, Ltd.), and the others (d) Mevalotin Tablets 5 mg, 10 mg, Mevalotin Fine Granules 0.5%, 1% (Daiichi Sankyo Co., Ltd.), and the others (e) Lochol Tablets 10 mg, 20 mg, 30 mg (Novartis Pharma K.K.), and the others (f) Crestor Tablets 2.5 mg, 5 mg, Crestor OD Tablets 2.5 mg, 5 mg (AstraZeneca K.K.)
Therapeutic category	Hyperlipidaemia agents
Indications	(a), (c), (e)-(f) Hypercholesterolemia, familial hypercholesterolemia (b), (d) hyperlipidemia, familial hypercholesterolemia

PRECAUTIONS (underlined parts are revised)

Important Precautions	<u>There have been reports of Immune-mediated necrotizing myopathy characterized by such as proximal muscle weakness, elevated CK (CPK), muscle fiber necrosis without inflammation, and anti-HMG-CoA reductase (HMGCR) antibody positive, which persisted despite discontinuation of treatment. Patients should be carefully monitored. Improvement in immune-mediated necrotizing myopathy has been reported after administration of immunosuppressive agents.</u>
Adverse reactions (clinically significant adverse reactions)	<u>Immune-mediated necrotizing myopathy: Immune-mediated necrotizing myopathy 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.</u>

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 3 months (April 2013 to July 2016).
Cases related to immune-mediated necrotising myopathy:
(a) 1 case (no fatal case)
(b) – (e) 0 case
(f) 1 case (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year:
(a) Approximately 3 600 000
(b) Approximately 410 000
(c) Approximately 1 950 000
(d) Approximately 1 650 000
(e) Approximately 250 000
(f) Approximately 5 420 000

Launched in Japan:
(a) May 2000
(b) December 1991
(c) September 2003 (Livalo Tab. 1 mg, 2 mg)
June 2012 (Livalo Tab. 4 mg)
July 2013 (Livalo OD Tab. 1 mg, 2 mg)
December 2013 (Livalo OD Tab. 4 mg)
(d) October 1989
(e) June 2003
(f) April 2005

(g) Amlodipine besilate/Atorvastatin calcium hydrate

Brand name (name of company)	(g) Caduet Combination Tablets No. 1, No. 2, No. 3, and No. 4 (Pfizer Japan Inc.), and the others
Therapeutic category	Miscellaneous cardiovascular agents
Indications	(g) This product is indicated for the following patients for whom treatment with both amlodipine and atorvastatin is appropriate: Patients with hypertension or angina pectoris, and concurrently with hypercholesterolemia or familial hypercholesterolemi

PRECAUTIONS (underlined parts are revised)

Important Precautions

There have been reports of Immune-mediated necrotizing myopathy characterized by such as proximal muscle weakness, elevated CK (CPK), muscle fiber necrosis without inflammation, and anti-HMG-CoA reductase (HMGCR) antibody positive, which persisted despite discontinuation of treatment. Patients should be carefully monitored. Improvement in immune-mediated necrotizing myopathy has been reported after administration of immunosuppressive agents.

Adverse reactions (clinically significant adverse reactions)

Immune-mediated necrotizing myopathy: Immune-mediated necrotizing myopathy 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.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 3 months (April 2013 to July 2016).
Cases related to immune-mediated necrotising myopathy:
(g) 0 case

The number of patients using the drug estimated by the MAH in the past 1 year:
(g) Approximately 380 000

Launched in Japan:
(g) December 2009

Case summary

No.	Patient		Daily dose	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Male 80s	Hypercholesterolaemia, hyperlipidaemia (fracture)	2.5 mg × 1 time/2 days Unknown 2.5 mg × 1 time/day Approximately 1 year	**Immune-mediated necrotising myopathy** Approximately 3 years before onset (Day 1 of administration) Treatment with rosuvastatin calcium 2.5 mg × 1 time/2 days (alternate-day regimen) was initiated. Silodosin, manidipine hydrochloride (10mg × 2 times/day), trimebutine maleate 100 mg, benexate hydrochloride betadex 200 mg, teprenone 50 mg, non-pyrine common cold drug, killed Escherichia coli (E. coli)/ hydrocortisone, oxethazaine, and rabeprazole sodium (1 time/day) were used concomitantly. Blood tests were performed once every 3 months. Approximately 1 year before onset Dosage of rosuvastatin calcium was increased to 2.5 mg × 1 time/day. Approximately 4 months before onset No abnormalities observed during regular health check-up. Alanine aminotransferase (ALT) was 27 IU/L and aspartate aminotransferase (AST) was 26 IU/L. 16 days before discontinuation Blood tests performed at a different hospital, Hospital A, showed increase in liver enzymes (AST: 301 IU/L, ALT: 251 IU/L). Approximately 3 years after beginning administration (Day of onset) The patient experienced difficulty in walking. The patient wobbled when walking and gradual muscular weakness was confirmed as the patient would fall frequently without a cane. The patient realized gait disturbance. Heaviness in both buttocks appeared when the patient was in a standing posture. Same month as onset (Day of discontinuation) The patient was referred to and consulted a gastroenterologist in Hospital A (abdominal echo and abdominal CT showed results that were within normal limits). While oral administration of rosuvastatin calcium was discontinued due to considerations for adverse reactions, the patient gradually worsened. In addition, the patient needed to rest once when moving from the hospital entrance to the consultation room. The patient regularly visited Hospital A for physical therapy and also continued to consult the orthopedic surgeon in the original hospital. The patient was orally administered tramadol hydrochloride/acetaminophen combination

				tablet and pregabalin. Approximately 2 months after discontinuation Consulted orthopedic surgeon at original hospital. While the physician pointed out spinal column stenosis in the C3/4-6/7 vertebrae and intervertebral disc hernia in the C6/7 vertebrae, the patient was placed under observation since no muscular weakness was observed. The patient was referred to and consulted a neurologist for the first time in order to exclude central nervous system disorders. Mild muscular weakness in both proximal lower limb muscles and notable oedema in both lower limbs. While tests for hypoproteinaemia, deep vein thrombosis, cardiac failure, etc. were performed, no abnormalities were observed and a rheumatologist was consulted as rheumatic diseases such as remitting seronegative symmetrical synovitis with pitting edema was considered. 85 days after discontinuation Blood tests performed in the rheumatology department indicated high levels of CK (7 874 IU/L), and the patient was admitted to the hospital for further testing as polymyositis (PM) and myopathy were suspected. The patient was able to walk when he was admitted to the hospital. No shoulder pain was observed. The patient already suffered from haemorrhoids and a major prolapse of haemorrhoids occurred during hospitalization. Treatment with killed E. coli/ hydrocortisone suppository twice daily was initiated. Ulcers were not observed using a gastroscope. 89 days after discontinuation The patient was transferred to the neurology ward as PM was suspected. Approximately 3 months after discontinuation (3rd week of hospitalization) Muscular weakness/muscle atrophy with severe muscular pain in the superior proximal limb muscles rapidly progressed. The patient was unable to remain seated and suffered from aphagia and severe dyslalia making speech incomprehensible. Given the extremely severe pain and no inflammatory background found in physical findings or blood tests (with no increase in body temperature as well), the patient was suspected to have statin-related myopathy instead of PM as it had been over 3 years since oral administration of statin was initiated and a muscle biopsy was performed. Similar to the clinical symptoms, results of the muscle biopsy did not confirm infiltration of inflammatory cells. Given that active necrosis regeneration was observed, the patient was diagnosed with necrotising myopathy. Results were negative for anti-aminoactyl transfer ribonucleic acid synthetase (ARS) antibodies and anti-signal recognition particle (SRP) antibodies. Haemorrhoids shrunk and it was no longer associated with pain or prolapse.

				112 days after discontinuation While 2 courses of steroid pulse therapy were administered, the patient exhibited a poor response to the treatment. High dose (HD) intravenous immunoglobulin (IVIg) therapy was used. 114 days after discontinuation (Day 3 after initiating IVIg) Pain dissipated drastically. 133 days after discontinuation (Week 4 after initiating IVIg) Normalization of CPK. Muscle strength and muscle mass gradually resolved. Approximately 6 months after discontinuation While pain and muscular weakness was not observed, CPK worsened to levels in the 800 range. The second IVIg was administered. Rash associated with pruritus, exfoliation, and mild redness appeared on the palm, torso, and upper limbs. The patient was placed under observation after being prescribed steroid ointments and epinastine hydrochloride. CPK levels resolved to less than 200. Dysphagia and dyslalia also completely resolved. Mild muscular weakness in the proximal muscles of the upper and lower limbs remained and the patient was not completely able to climb up and down the stairs (was going through rehabilitation exercises). Date unknown As necrotizing myopathy resolved, activities of daily living (ADL) improved. Due to over use of both upper limbs, joint pain in both shoulders were seen. Lidocaine and steroids were injected into the joints by the orthopedic surgeon in the original hospital. Treatment with proton pump inhibitors was restarted. No black stool was observed. 252 days after discontinuation Before the patient was discharged from the hospital, lidocaine and steroids were locally injected into both shoulder joints. Approximately 8 months after discontinuation The patient was able to walk and was discharged from the hospital. 256 days after discontinuation The patient transferred hospitals to Hospital B for rehabilitation purposes. Requests to continue twice daily killed E. coli/ hydrocortisone administration was made. At time of discharge, ADL of the proximal muscles of the upper and lower limbs was approximately -1 and the patient was able to walk stably using a walker. The patient had no waddling gait, and muscular weakness in distal muscles was not confirmed. Dysphagia and dyslalia was not confirmed. Bladder and rectal disturbance was not confirmed. Hospital C was requested to perform tests to measure anti-SRP antibodies and anti-HMGCR antibodies. The patient tested positive for anti-HMGCR

				antibodies, and confirmed diagnosis was therefore anti-HMGCR antibody positive myopathy. Oral steroids were not administered considering the patient's age and non-responsiveness towards pulse therapy. Approximately 10 months after discontinuation Although anti-HMGCR antibody positive myopathy resolved, myopathy (muscular weakness) resolved with sequelae. The patient was discharged from Hospital B.
	Concomitant medications: Silodosin, manidipine hydrochloride, trimebutine maleate, benexate hydrochloride betadex, teprenone, non-pyrine common cold drug, killed E. coli/hydrocortisone, oxethazaine, rabeprazole sodium			

Laboratory examination

Test item	Unit	85 days after discontinuation	116 days after discontinuation	144 days after discontinuation	Approximately 6 months after discontinuation	Approximately 6 months after discontinuation (2nd time)	319 days after discontinuation
CPK	IU/L	7 874	672	155	In the 800s	Less than 200	93

	Test method	Results
Anti-HMGCR antibody (222 days after discontinuation)	Enzyme-linked immunosorbent assay (ELISA)	Positive

2 Ustekinumab (genetical recombination)

Brand name (name of company)	Stelara Subcutaneous Injection 45 mg Syringe (Janssen Pharmaceutical K.K.)
Therapeutic category	Miscellaneous metabolism agents-Miscellaneous
Indications	The following diseases with an inadequate response to conventional therapy: Psoriasis vulgaris, Psoriatic arthritis

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

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

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 4 months (April 2013 to August 2016).
Cases related to interstitial pneumonia: 6 case (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 3 800

Launched in Japan: March 2011

Case summary

No.	Patient		Daily dose	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Male 70s	Psoriasis (None)	45 mg 32 weeks (dosing interval unknown)	**Interstitial pneumonia** Day 1 of administration Treatment with ustekinumab was initiated. 32 weeks after initiating administration Ustekinumab administered (last administration). 52 days after last administration Regularly consult a dermatologist. The patient complained of general malaise and coughing as subjective symptoms that occurred from about a week ago. 53 days after last administration Consulted a pulmonologist. Findings from chest CT scan: Ground-glass opacity found in the medial-basal segment, lower lateral lobe, and upper lobe of the right lung. Granular shadow was observed over a large portion of the lung field. Drug-induced pneumonia caused by ustekinumab was suspected. Benproperine phosphate was prescribed. 61 days after last administration No improvement was seen in coughing, and the patient consulted the hospital due to severe malaise after which he was admitted to the hospital. Treatment with dextromethorphan hydrobromide hydrate and codeine phosphate hydrate (taken as needed). Steroid pulse therapy, artificial respirator, oxygen administration, etc. were not used. 63 days after last administration

				Bacteria was not detected in sputum smears (gram staining) and cultures (+susceptibility testing). Cytomegalovirus related tests (polymerase chain reaction [PCR] or blood antigen/antibody reaction) were negative. 67 days after last administration Findings from bronchoscopic lung biopsy: Foreign-body giant cells with interstitial cholesterin inside the cell were found in parts of the alveolar lumina. Significant fibrosis or interstitial infiltration of inflammatory cells were not observed. Bronchoalveolar lavage fluid tests were performed. Cell count: 5.5×10^6, lymphocytes: 49.1%, neutrophils: 0.3%, eosinophils (Eos): 7.0%, basophils: 1.7%, macrophages: 41.8%. The patient was determined to have drug-induced pneumonia due to ustekinumab based on episodes, findings from imaging diagnostics and bronchoscopic test results. Pneumocystis related tests (PCR) were negative. 80 days after last administration Resolving based on chest CT scan results. Subjective symptoms were also resolving slightly. 87 days after last administration No changes were observed even after provocation tests back at home was performed. 94 days after last administration Anti-Smith antibodies (<10.0 U/mL): (-) Anti-topoisomerase 1 antibodies (<10.0 U/mL): (-) Anti-deoxyribonucleic acid antibodies (0-6 IU/mL): 4 IU/mL Anti-centromere antibodies (0-10 U/mL): <2.0 U/mL ARS antibodies (-): (-) 95 days after last administration The patient was discharged from the hospital and follow-up was conducted on an outpatient basis. Outcome: resolving
	Concomitant medications: None			

Laboratory examination

Test item	14 days before administration	61 days after last administration	84 days after last administration	88 days after last administration	94 days after last administration	116 days after last administration
WBC (/mm^3)	6 500	3 700	-	-	3 600	-
CRP (mg/dL)	0.10	0.08	-	-	8.9	-
KL-6 (U/mL)	-	1 223	1 281	-	-	1 018
SP-A (ng/mL)	-	-	37.9	-	-	-
SP-D (ng/mL)	-	-	420	-	-	-
PaO2 (Torr)	-	80.5	-	82.7	-	-

3 Nivolumab (genetical recombination)

Brand name (name of company)	Opdivo Intravenous Infusions 20 mg, 100 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics – Miscellaneous
Indications	Radically unresectable malignant melanoma Unresectable, advanced, or relapsed non-small cell lung cancer Radically unresectable or metastatic renal cell carcinoma

PRECAUTIONS (underlined parts are revised)

Important Precautions

Various diseases or conditions may occur due to excessive immunoreaction caused by T cell activation effect of nivolumab. Patients should be carefully monitored. If any abnormalities are observed, appropriate differential diagnosis should be conducted taking into consideration that the adverse reaction may be caused by excessive immunoreaction. If adverse reaction due to excessive immunoreaction are suspected, appropriate measures such as administration of adrenal corticosteroids should be considered. Serious adverse reactions may occur after discontinuation of treatment with nivolumab. The patient should continue to be carefully monitored even after discontinuation of treatment with nivolumab.

Adverse reactions (clinically significant adverse reactions)

Immune thrombocytopenic purpura (ITP): ITP may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of nivolumab should be discontinued and appropriate measures should be adopted.

Myasthenia gravis, myocarditis, myositis, rhabdomyolysis: Myasthenia gravis, myocarditis, myositis, or rhabdomyolysis may occur, and there have been reports of cases where these complications have occurred. Muscular weakness, eyelid ptosis, dyspnoea, dysphagia, increased CK (CPK), abnormal electrocardiogram, and increased blood/urine myoglobin, etc. should be carefully monitored. If any abnormalities are observed, administration of nivolumab should be discontinued, and appropriate measures such as administration of adrenal corticosteroids should be adopted. In addition, aggravations of respiratory conditions should be carefully monitored as respiratory failure may progress rapidly due to the myasthenia gravis crisis.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 4 months (April 2013 to August 2016).
(a) Cases related to reported cases of adverse reaction after discontinuation of administration: 14 case (no fatal case)
(b) Cases related to ITP: 3 case (no fatal case)
(c) Cases related to myocarditis: 3 case (1 fatal case)
(d) Cases related to rhabdomyolysis: 4 case (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 8 200

Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Female 70s	Malignant melanoma (Hypertension, hyperlipidaemia, meningioma)	2 mg/kg Twice every 3 weeks	**ITP, hyperthyroidism, decreased thyroid function, multiple cerebral infarction** 1 year and 5 months before administration First consultation. Confirmed malignant melanoma (primary site: sole of the left lower limb [heel]). 1 year and 4 months before administration Tumor excision of the left sole and lymph node dissection of the left inguinal region were performed. 1 year and 3 months before administration Treatment with 6 courses of dacarbazine, nimustine hydrochloride, vincristine, and interferon beta therapy was initiated. 7 months before administration 2 courses of interferon beta maintenance therapy (interferon localized therapy) was initiated. 2 months before administration Induction with nivolumab considered as lung metastasis and hilar lymph node metastasis was confirmed. Day 1 of administration Negative for BRAF gene mutation. 2mg/kg of nivolumab administered for radically unresectable malignant melanoma. 24 days after administration (Day of discontinuation) Administer nivolumab for the second time. Hyperthyroidism was confirmed but the patient had no subjective symptoms and administration with nivolumab was continued. No other procedures were conducted. 19 days after discontinuation Purpura in the lower limbs as well as gingival bleeding occurred. The patient decided to observe the symptoms at home. 21 days after discontinuation The patient visited the hospital to receive the third dose of nivolumab. Administration of nivolumab was discontinued as platelet (PLT) count notably decreased to 2 000/μL, and the patient was emergently admitted to the hospital. Treatment with 10U of platelet concentrate was initiated (administered 10-20 U subsequently until 33 days after discontinuation). Hematologist was consulted. Although gingival bleeding was observed, the patient had no subjective symptoms. Hyperthyroidism resolved. 22 days after discontinuation Treatment with methylprednisolone 250 mg and oral prednisolone 40 mg/day was initiated. Administration of furosemide was initiated. 23 days after discontinuation Dosage of methylprednisolone was decreased to 125 mg. 24 days after discontinuation No increase in PLT. Treatment with HD IVIg 400 mg/kg/day × 5 days initiated. 25 days after discontinuation Gingival bleeding and melena (stool appearance: black stool + bloody stool). 26 days after discontinuation The patient was fasted and placed on fluid management and bed rest management due to melena. Mild malaise

				observed. Lansoprazole initiated for bleeding and protection from steroid use. 28 days after discontinuation Evidence of gastrointestinal haemorrhage found during endoscopic examinations. Hemoglobin (Hb) was 6.8 g/dL and was resolving due to administration of 2 U of red blood cell concentrates. PLT remained at 2 000/μL and did not resolve; treatment with romiplostim 60 μg/day was initiated. Positive for anti-platelet antibodies. Confirmed diagnosis for ITP as the patient did not demonstrate any signs of infection or autoimmune disease. 30 days after discontinuation Malaise and melena disappeared. 31 days after discontinuation Gingival bleeding disappeared. 33 days after discontinuation Re-initiate food intake. 35 days after discontinuation Negative for Helicobacter pylori antigens in the stool. Administered romipostim 120 μg/day as treatment for ITP. 42 days after discontinuation Administer romipostim 120 μg/day. Decreased thyroid function confirmed. No subjective symptoms were observed and the patient was administered levothyroxine 25 μg as treatment. 43 days after discontinuation Purpura disappeared. The patient presented with slurred speech, difficulty speaking, and mild paralysis in right upper and lower limbs. Treatment with heparin 1 000 U/day was initiated. 44 days after discontinuation The patient was diagnosed with multiple cerebral infarction based on magnetic resonance imaging (MRI) scans. 45 days after discontinuation PLT resolved to 90 000/μL. 47 days after discontinuation Dosage of prednisolone decreased to 30 mg/day. 51 days after discontinuation Speaking abilities resolved. Paralysis was resolving. Difficult for the patient to carry out detail-oriented tasks; therefore, meals were taken using a spoon. Complete administration with heparin. 52 days after discontinuation PLT was 124 000/μL, a sufficient level for PLT, and ITP resolved. 54 days after discontinuation PLT resolved to 120 000/μL. Dosage of prednisolone was decreased to 25 mg/day. Gastrointestinal haemorrhage also stabilized. 59 days after discontinuation Decreased thyroid function was resolving. 66 days after discontinuation Multiple cerebral infarction resolved with sequelae. 132 days after discontinuation Complete administration with prednisolone.
	Concomitant medications: Amlodipine besilate, pravastatin sodium			

Laboratory examination

Test item	12 days before administration	Day of discontinuation	21 days after discontinuation	24 days after discontinuation	26 days after discontinuation	33 days after discontinuation	34 days after discontinuation	35 days after discontinuation	43 days after discontinuation	44 days after discontinuation	45 days after discontinuation	59 days after discontinuation	66 days after discontinuation
TSH (mU/L)	2.18	0.022	0.189	−	−	−	−	−	−	−	−	34.3	−
FT3 (pg/mL)	2.51	9.99	2.23	−	−	−	−	−	−	−	−	1.42	−
FT4 (ng/dL)	1.29	6.12	1.13	−	−	−	−	−	−	−	−	0.496	−
WBC (10 000/μL)	0.544	0.44	0.532	1.19	0.91	0.864	0.781	0.742	0.58	0.75	0.562	0.454	0.296
RBC (10 000/μL)	400	383	419	331	272	311	313	314	307	323	339	366	353
Hb (g/dL)	12.8	12.2	13.2	10.7	8.7	10.0	10.1	10.1	10.1	10.6	11.2	11.6	11.3
PLT (10 000/μL)	22.8	19.6	0.2	0.1	0.2	0.7	1.7	4.2	9.1	8.8	9	18	19.9
CRP (mg/dL)	0.2	0.3	0.4	−	0.1>	−	0.0	−	0.1>	−	−	0.1	0.1
Lym (%)	−	27.5	22.6	24.7	−	−	19.5	−	16.3	19.4	19	−	−
APTT (sec)	−	22	29.2	−	−	−	25.4	−	24.5	46.7	66.8	−	−
PT (%)	−	11.5	11.5	−	−	−	11.1	−	12.1	12.4	11.9	−	−
PT (INR)	−	0.97	0.98	−	−	−	0.95	−	1.04	1.06	1.03	−	−
FDP (μg/mL)	−	−	−	−	−	−	1.7	−	1.3	0.9	0.7	−	−
Fib (mg/dL)	−	−	−	−	−	−	189	−	110	104	159	−	−
PLT surface IgG	−	−	−	−	0.75	−	−	−	−	−	−	−	−

<Autoantibody related tests> Performed 27 days after discontinuation
Anti-PLT antibodies: positive, PLT-related immunoglobulin G: 4 450.7 ng/10^7 cells, soluble interleukin-2 receptors: 1 170 U/mL, anti-SS-A/Ro antibodies: 27.3 U/mL, antinuclear antibodies (ELISA): 22.8 times

Case summary

No.	Patient		Daily dose	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
2	Male 60s	Recurrent non-small cell lung cancer (Pleural effusion)	3 mg/kg Twice every 2 weeks	**Myocarditis, myasthenia gravis** 2 years before administration Radiotherapy (whole-brain) and 4 courses of carboplatin + pemetrexed (CBDCA + PEM) was conducted. 1 year and 8 months before administration 5 courses of PEM maintenance therapy conducted. 1 year and 6 months before administration Radiotherapy (lumbar spine) and 18 courses of docetaxel + bevacizumab was conducted. 2 months before administration Progression of primary disease confirmed in positron emission tomography-CT scans. Day 1 of administration Treatment with nivolumab (3 mg/kg) initiated. 14 days after administration (Day of discontinuation) Second dose of nivolumab administered. 14 days after discontinuation The patient visited the hospital after suffering from back pain, general malaise, elevated cardiac enzymes, and precordial ST elevation from 2-3 days before. Blood pressure: 76/34 mmHg, pulse: 102 times/minute, oxygen saturation: 95%, and body temperature: 36.0°C. The patient also presented with difficulty in articulation and decreased conscious level; a head/chest CT was performed. Bone

				metastasis (spine and ribs) seen. No brain metastasis. Bilateral pleural effusion and carcinomatous pleurisy was observed. The patient was admitted to the hospital due to deteriorating cardiovascular function. Emergency cardiac catheter test: Asynergy mainly found in apical region and the inferior wall was dyssynchronic. Administration of carperitide continuous infusion was initiated to treat cardiac failure. Right eyelid ptosis, nuchal rigidity, and difficulty in walking observed. Pupil diameter: 3.5/3.5 mm, light reflex: +/+, slightly slow in both eyes. Extraocular movement test: Both eyes only move slightly. Dysarthria and muscular weakness in all four limbs observed. Deep tendon reflex test: Weak to diminished in all four limbs. The patient was diagnosed with myasthenia gravis and myositis due to use of nivolumab. Steroid pulse therapy (for 3 days → post-therapy [approximately 1 mg/kg]) was initiated. Electrocardiogram: Complete right bundle branch block type QRS and complete left bundle branch block type QRS. Cardiac ultrasonography test: dilated inferior vena cava (IVC), diameter 29 mm, tricuspid regurgitation (TR): 1/4, and TR pressure gradient: 14 mmHg. Beta-blockers were administered to treat sporadic premature ventricular contractions, and bisoprolol tape 4mg was used as a patch. The patient did not respond to steroid pulse therapy with 1 000 mg. Left ventricular ejection fraction was 44%. Dilated IVC +. Slight pericardial effusion +. Pleural effusion +. 15 days after discontinuation Pulseless ventricular tachycardia occurred, and the patient resumed spontaneous circulation after a defibrillator was used. Amiodarone continuous infusion was initiated as the patient was suspected to have ventricular arrhythmia caused by drug-induced myocarditis. Percutaneous cardiopulmonary support (PCPS)/intra-aortic balloon pump support were initiated due to ventricular tachycardia and circulatory breakdown. Myocardial biopsy was performed. Endotracheal intubation and artificial respirator started. The patient was diagnosed with severe myocarditis and myasthenia gravis due to nivolumab. Plasma exchange initiated. 16 days after discontinuation Steroid pulse therapy and plasma exchange conducted. 17 days after discontinuation Oral prednisolone 60 mg/day administered and plasma exchange conducted. 19 days after discontinuation HD IVIg administered for myasthenia gravis. On-off test was performed for myocarditis, and dopamine/dobutamine was administered concurrently. Spontaneous cardiac contraction was resolving; therefore, PCPS was removed. Both heart beat and blood pressure stabilized and no issues were observed. 22 days after discontinuation High-rate, persistent ventricular tachycardia was observed, and blood pressure drastically decreased. Sinus rhythm was resumed using a defibrillator. 26 days after discontinuation Oral administration of prednisolone 50 mg/day. 27 days after discontinuation Staphylococcus was detected in blood culture, Pseudomonas aeruginosa in sputum culture: +3. Sulbactam/ampicillin → ceftazidime was administered. 28 days after discontinuation

				Administration of vancomycin was initiated. 30 days after discontinuation Prednisolone 40 mg administered. 33 days after discontinuation Tracheotomy performed. 34 days after discontinuation Prednisolone 30 mg administered. The patient was transferred to the pulmonology ward. 37 days after discontinuation Prednisolone 20 mg administered. 40 days after discontinuation Prednisolone 10 mg administered. 43 days after discontinuation Ringer acetate solution was administered with a fully open drip as the patient's blood pressure continued to drop. Noradrenaline 3A + saline solution 47 mL was initiated at 5 mL/hr. TR: -, mitral regurgitation: -, aortic regurgitation: -, notable enlargement of the right heart system and dilated IVC. 46 days after discontinuation Initiate administration of prednisolone 1 000 mg. Brainwave test: low voltage slow wave, similar voltage observed overall in general suggesting large scale cerebral disorder. 49 days after discontinuation Continuing pulse therapy was deemed impossible; therefore, dosage of prednisolone was decreased to 60 mg. 55 days after discontinuation Candida detected in blood culture. Administration of micafungin sodium 150 mg/day was initiated to treat candidaemia. 63 days after discontinuation Spontaneous respiration decreased and the patient was switched to a mechanical ventilator. The patient suffered from ventricular fibrillation, and while chest compressions, attachment of an automated external defibrillator, and administration of adrenaline were performed, the patient died from fatal arrhythmia associated to myocarditis. Myasthenia gravis was determined to leave sequela.
	Concomitant medications: Atorvastatin calcium hydrate, torasemide, non-pyrine common cold drugs			

Laboratory examination

Test item	Day 1 of administration	14 days after discontinuation	27 days after discontinuation	43 days after discontinuation	63 days after discontinuation
CPK (IU/L)	26	9892	−	−	−
CK-MB (U/L)	−	325	−	−	54
CRP (mg/dL)	0.2	3.4	0.7	5.4	0.2
WBC (10 000/μL)	0.41	0.75	1.05	0.75	0.66
Neu (%)	68.0	80.4	90.3	87.0	−
Eos (%)	2.7	0.1	0.0	0.4	−
Lym (%)	24.0	14.4	7.2	7.6	37.0
PLT (10 000/μL)	7.9	16.2	5.3	9.4	3.4
AST (IU/L)	23	657	25	33	144
ALT (IU/L)	13	297	20	76	658
LDH (IU/L)	267	2120	402	373	913
IgG (mg/dL)	−	1390	−	−	−
IgM (mg/dL)	−	72	−	−	−
Semi-quantitative urine protein (mg/dL)	−	30	−	−	−
Troponine I (ng/mL)	−	39.82	−	−	−

<Histopathology of myocardial biopsy> (15 days after discontinuation)
Histopathological findings: Severe acute myocarditis image (location unknown)
Immunohistochemical findings: Multiple cluster of differentiation (CD) 3 and CD45RO positive T-cells. Possible autoimmune myocarditis after administration of anti-programmed cell death protein-1 antibody.

Case summary

No.	Patient		Daily dose	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
3	Female 70s	Recurrent non-small cell lung cancer (None)	3 mg/kg Twice every 2 weeks	**Rhabdomyolysis, elevated CPK, increased eosinophil count, myositis** Date unknown The patient was confirmed to have non-small cell lung cancer. 4 months before administration Chemotherapy (CBDCA + PEM) was initiated. 1 month before administration Chemotherapy (CBDCA + PEM) was completed. Day 1 of administration Defined to have progressive disease, and administration of nivolumab 3 mg/kg was initiated to treat unresectable, progressive/recurrent non-small cell lung cancer. Day 14 of administration (Day of discontinuation) Second dose of nivolumab administered. 14 days after discontinuation In tests performed before administration of the third dose of nivolumab, results indicated elevated CPK, eosinophil count, lactate dehydrogenase (LDH), AST, and ALT, and presented with symptoms for myalgia. The patient was admitted to the hospital due to suspicion of nivolumab-induced myalgia and rhabdomyolysis. Fluid replacement therapy was conducted and the patient was placed under observation. Administration of nivolumab was discontinued. Date unknown: Muscle MRI findings: Presence of echo signals. 17 days after discontinuation CPK and hepatic function levels did not resolve after fluid replacement. Steroid pulse therapy (for 3 days) was conducted. 20 days after discontinuation Administration of oral prednisolone 40 mg/day was initiated. 42 days after discontinuation CPK was normalizing and increasing eosinophil count was resolving. 45 days after discontinuation CPK decreased until normal values and myalgia disappeared. Elevated CPK, rhabdomyolysis, and myositis resolved. Dosage of oral prednisolone was decreased. 52 days after discontinuation The patient was discharged from the hospital after it was determined that the patient continue to take steroids at the decreased dose on an outpatient basis. Dosage of prednisolone was decreased to 15 mg/day.
	Concomitant medications: Antibiotic-resistant lactic acid bacteria preparation (3), brotizolam			

Laboratory examination

Test item	7 days before administration	Day of discontinuation	14 days after discontinuation	17 days after discontinuation	21 days after discontinuation	24 days after discontinuation	28 days after discontinuation	31 days after discontinuation	38 days after discontinuation	42 days after discontinuation	45 days after discontinuation	52 days after discontinuation
CPK (IU/L)	46	−	8382	8631	1310	770	488	361	264	211	183	163
LDH (IU/L)	−	180	1199	1477	1310	1068	−	636	519	428	404	370
Neu (%)	−	−	46.4	−	−	−	−	−	−	87.1	−	−
AST (IU/L)	−	31	450	542	140	70	−	51	45	41	36	35
ALT (IU/L)	−	15	221	286	265	192	−	110	86	78	72	51
WBC (10 000/μL)	−	−	0.69	−	−	−	−	−	−	0.93	−	−
Eos (%)	−	−	7.2	−	−	−	−	−	−	0.0	−	−
CK-MB (IU/L)	−	−	292.7	305.5	83.3	195.6	188.7	164.6	121.5	−	88.5	77.2
BUN (mg/dL)	15.1	−	18.1	12.0	24	26.9	23.2	22.6	22.5	−	18.1	18.8
Cr (mg/dL)	0.54	−	0.56	0.48	0.46	0.43	0.41	0.44	0.41	−	0.40	0.47
Occult blood in urine	(-)	−	(2+)	(2+)	(+/-)	(-)	(-)	(-)	(-)	−	(-)	(-)

<Autoantibody related tests> (Dates unknown)
Anti-histidyl-1 ribonucleic acid synthetase antibodies: negative, anti-ARS antibodies: negative

5

Revision of Precautions (No. 279)

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 18, 2016.

1 Anticoagulants

Warfarin potassium

Brand name	Warfarin Tablets 0.5 mg, 1 mg, 5 mg, Warfarin Granules 0.2% (Eisai Co., Ltd.), and the others
Contraindications	Patients receiving miconazole (gel, injection)
Contraindications for Concomitant Use	Miconazole (gel, injection)

2 Acting mainly on mold / Miscellaneous chemotherapeutics

(a) Itraconazole
(b) Fluconazole
(c) Fosfluconazole
(d) Voriconazole

Brand name	(a) Itrizole Capsules 50 mg, Itrizole Oral Solution 1%, Itrizole Injection 1% (200 mg) (Janssen Pharmaceutical K.K.), and the others (b) Diflucan Capsules 50 mg, 100 mg, Diflucan Dry Syrup 350 mg, 1400 mg, Diflucan Intravenous Solution 50 mg, 100 mg, 200 mg (Pfizer Japan Inc.), and the others (c) Prodif Intravenous Solution 100 mg, 200 mg, 400 mg (Pfizer Japan Inc.) (d) Vfend Tablets 50 mg, 200 mg, Vfend Dry Syrup 2800 mg, Vfend Intravenous Solution 200 mg (Pfizer Japan Inc.), and the others
Careful Administration	Patients receiving warfarin.
Important Precautions	A marked increase in INR resulting from increased effects of warfarin has been reported in patients receiving the product concomitantly with warfarin. Whether a patient takes warfarin must be confirmed before initiating treatment with the product. In case of concomitant use with warfarin, extreme caution should be exercised during administration by taking adequate measures such as increasing the frequency of PT measurement and thrombotest.

3 **Miscellaneous chemotherapeutics**

Miconazole

Brand name	Florid Oral Gel 2%, Florid-F 200 mg for Injections (Mochida Pharmaceutical Co., Ltd.)
Contraindications	Patients receiving warfarin potassium
Contraindications for Concomitant Use	Warfarin potassium

4 **Acting mainly on gram-positive bacteria**

Daptomycin

Brand name	Cubicin I.V. 350 mg (MSD K.K.)
Adverse reactions (clinically significant adverse reactions)	Acute generalized exanthematous pustulosis: Acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

5 **Antivirals**

Peramivir hydrate

Brand name	Rapiacta 300 mg Bag for Intravenous Drip Infusion, Rapiacta 150 mg Vial for Intravenous Drip Infusion (Shionogi & Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	Acute renal failure: Acute renal failure may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

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 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 September 30, 2016)

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

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Brodalumab (Genetical Recombination) Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Hakko Kirin Co., Ltd.	September 30, 2016
◎	Adalimumab (Genetical Recombination) Humira for SC Injection 40 mg syringe 0.8 mL, 40 mg syringe 0.4 mL, 80 mg syringe 0.8 mL[*1]	AbbVie GK	September 28, 2016
◎	Aripiprazole Abilify Tablets 1 mg, 3 mg, 6 mg, 12 mg, OD Tablets 3 mg, 6 mg, 12 mg, powder 1%, oral solution 0.1%[*2]	Otsuka Pharmaceutical Co., Ltd.	September 28, 2016
◎	Propranolol Hydrochloride Hemangiol Syrup for Pediatric 0.375%[*3]	Maruho Co., Ltd.	September 16, 2016
◎	Progesterone OneCrinone 90 mg Progesterone Vaginal Gel	Merck Serono Co., Ltd.	September 7, 2016
◎	Alirocumab (Genetical Recombination) Praluent Subcutaneous Injection pen 75 mg, 150 mg, Syringe 75 mg, 150 mg	Sanofi K.K.	September 5, 2016
◎	Levodopa/Carbidopa Hydrate Duodopa enteral combination solution	AbbVie GK	September 1, 2016
	Lacosamide Vimpat Tablets 50 mg, 100 mg	UCB Japan Co. Ltd.	August 31, 2016
	Sodium Picosulfate Hydrate, Magnesium Oxide, Anhydrous Citric Acid Picoprep Combination Powder	Ferring Pharmaceuticals Co., Ltd.	August 31, 2016
	Carfilzomib Kyprolis Intravenous Infusions 10 mg, 40 mg	ONO Pharmaceutical Co., Ltd.	August 31, 2016
	Nivolumab (Genetical Recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*4]	ONO Pharmaceutical Co., Ltd.	August 26, 2016
	Remifentanil Hydrochloride Ultiva Intravenous 2 mg, 5 mg[*5]	Janssen Pharmaceutical K.K.	August 26, 2016
	Vigabatrin Sabril 500mg Powder	Sanofi K.K.	July 27, 2016

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Fumarate Genvoya Combination Tablets	Japan Tobacco Inc.	July 8, 2016
Octocog Beta (Genetical Recombination) Kovaltry for iv injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin, Ltd.	June 29, 2016
Bexarotene Targretin Capsules 75 mg	Minophagen Pharmaceutical Co., Ltd.	June 23, 2016
Maxacalcitol/betamethasone butyrate propionate Marduox Ointment	Chugai Pharmaceutical Co., Ltd.	June 21, 2016
Primaquine Phosphate Primaquine Tablets 15 mg	Sanofi K.K.	June 17, 2016
Dutasteride (1) Zagallo Capsules 0.1 mg (2) Zagallo Capsules 0.5 mg	GlaxoSmithKline K.K.	June 13, 2016
Mepolizumab (Genetical Recombination) Nucala for Subcutaneous Injection 100 mg	GlaxoSmithKline K.K.	June 7, 2016
Radium (^{223}Ra) Chloride Xofigo Injection	Bayer Yakuhin, Ltd.	June 1, 2016
Rurioctocog Alfa Pegol (Genetical Recombination) Adynovate Intravenous 250, 500, 1000, 2000	Baxalta Japan Ltd.	June 1, 2016
Trametinib Dimethyl Sulfoxide Mekinist Tablets 0.5mg, 2mg	Novartis Pharma K.K.	June 1, 2016
Dabrafenib Mesilate Tafinlar Capsules 50mg, 75mg	Novartis Pharma K.K.	June 1, 2016
Perampanel Hydrate Fycompa Tablets 2 mg, 4 mg	Eisai Co., Ltd.	May 26, 2016
Asenapine Maleate Sycrest Sublingual Tablets 5 mg, 10 mg	Meiji Seika Pharma Co., Ltd.	May 26, 2016
Sebelipase Alfa (Genetical Recombination) Kanuma Injection for Intravenous 20 mg	Alexion Pharma G.K.	May 25, 2016
Osimertinib Mesilate Tagrisso Tablets 40 mg, 80 mg	AstraZeneca K.K.	May 25, 2016
Ceritinib Zykadia Capsules 150 mg	Novartis Pharma K.K.	May 25, 2016
Ibrutinib Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	May 25, 2016
Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg[*6]	Teijin Pharma Limited	May 23, 2016
Botulinum Toxin Type A Botox Vista Injection 50 Units[*7]	Allergan Japan K.K.	May 23, 2016
Iloprost Ventavis Inhalation Solution 10 μg	Bayer Yakuhin, Ltd.	May 16, 2016
Methacholine Chloride (1) Provocholine Powder for Inhalation Solution 100 mg (2) Kenbran Powder for Inhalation Solution 100 mg	(1) Sanwa Kagaku Kenkyusho Co., Ltd. (2) Santen Pharmaceutical Co., Ltd.	May 10, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
	Nonacog Gamma (Genetical Recombination) Rixubis Intravenous 250, 500, 1000, 2000, 3000	Baxter Limited	May 9, 2016
	Luliconazole Luconac Solution 5% *8	Sato Pharmaceutical Co., Ltd.	April 25, 2016
	Progesterone Luteum Vaginal Suppository 400 mg	Aska Pharmaceutical Co., Ltd.	April 21, 2016
	Evolocumab (Genetical Recombination) Repatha SC Injection 140 mg syringe, 140 mg pen	Amgen Astellas BioPharma K.K.	April 21, 2016
	Ibandronate Sodium Hydrate Bonviva Tablets 100 mg	Chugai Pharmaceutical Co., Ltd.	April 21, 2016

*1 Non-infectious intermediate, posterior and panuveitis
*2 Irritability associated with autism spectrum disorder in childhood
*3 Infantile haemangioma
*4 Radically unresectable or metastatic renal cell carcinoma
*5 Analgesia in maintaining general anesthesia of children
*6 Hyperuricemia associated with cancer chemotherapy
*7 Lateral canthal lines in adult patients under the age of 65
*8 Nail tinea