Pharmaceuticals and Medical Devices Safety Information

No. 332 April 2016

Table of Contents

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Available information is listed here

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No. 332 April 2016

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

[Outline of Information]

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

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

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

Abbreviations

ADR	Adverse drug reaction
BE	Base excess
C-ANCA	Cytoplasmic anti-neutrophil cytoplasmic antibody
C3	Complement 3
C4	Complement 4
CH50	50% hemolytic complement
Cl	Chloride
CL-β2GPI	Cardiolipin β2-glycoprotein I
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
DNA	Deoxyribonucleic acid
DPC	Diagnosis procedure combination
ds-DNA	Double stranded deoxyribonucleic acid
DVT	Deep vein thrombosis
EPPV	Early post-marketing phase vigilance
GAD	Glutamic acid decarboxylase
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
JDS	Japan Diabetes Society
JSMO	Japanese Society of Medical Oncology
Jo-1	Histidyl t- Ribonucleic acid synthetase
K	Potassium
KL-6	Krebs von den Lunge-6
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Na	Sodium
PE	Pulmonary embolism
PEHB	Pharmaceutical and Environmental Health Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PR3-ANCA	Proteinase 3 anti-neutrophil cytoplasmic antibody
Scl-70	Scleroderma-70
Sm	Smith
SS-A	Sjogren's-syndrome A
SS-B	Sjogren's-syndrome B
ss-DNA	Single stranded deoxyribonucleic acid
WBC	White blood cell

1

Notification Regarding Fulminant Type 1 Diabetes Mellitus During Use of Nivolumab (Genetical Recombination)

1. Introduction

Nivolumab (genetical recombination) (hereinafter referred to as “this drug”), brand name Opdivo Intravenous Infusions 20 mg and 100 mg, gained marketing approval in July 2014 for the indication “radically unresectable malignant melanoma” and was launched in September the same year.

Cases of type 1 diabetes mellitus including fulminant type 1 diabetes mellitus have been reported in patients treated with this drug in Japan. Therefore, cautionary warnings were released after revision of the package insert in November 2015.

Furthermore, it gained additional approval for the indication “unresectable advanced/recurrent non-small cell lung cancer” in December 2015, and was removed as a diagnosis procedure combination (DPC) target from February 2016; thus, the number of patients in which this drug will be prescribed is likely to increase. Based on the aforementioned situation, the Ministry of Health, Labour and Welfare (MHLW) released a “notification regarding fulminant type 1 diabetes mellitus during use of nivolumab (genetical recombination)” dated January 28, 2016. This section introduces the contents of the notification and relevant case summaries.

2. About Fulminant Type 1 Diabetes Mellitus

Of the various types of type 1 diabetes mellitus, fulminant type 1 diabetes mellitus particularly requires prompt detection and appropriate treatment since patients with this complication rapidly become severe such as begin suffering from ketoacidosis within 1 week after onset of diabetic symptoms and has the risk of being fatal if appropriate measures are not adopted.

As such, if there is a drastic increase in blood glucose levels or if diabetic symptoms such as thirst, polydipsia, polyuria, weight decrease, systemic malaise and disturbed consciousness is observed, prompt measures with sufficient supervision from diabetologists are necessary as fulminant type 1 diabetes mellitus can be suspected. Healthcare professionals are required to sufficiently inform patients regarding the possibility of fulminant type 1 diabetes mellitus and symptoms patients should pay attention to.

[Diagnostic criteria for fulminant type 1 diabetes mellitus (2012)]
(The Japan Diabetes Society [JDS])
Diagnosed as fulminant type 1 diabetes mellitus if fulfill all of the following attributes 1-3.

1. Suffers from ketosis or ketoacidosis within 1 week after onset of diabetic symptoms (either confirm positive urine ketone body at time of initial consultation or increase in blood ketone bodies).
2. (Random) blood glucose levels are ≤ 288 mg/dL (16.0 mmol/L) and HbA1c levels (NGSP) are <8.7%* at time of initial consultation.
3. Urine C peptide is <10 μg/day at time of disease onset, or fasting serum C peptide is <0.3 ng/mL and after glucagon loading (or 2 hours after meals) serum C peptide is <0.5 ng/mL.

*: If the patient already has abnormal glucose tolerance prior to onset of fulminant type 1 diabetes mellitus, these values may not necessarily apply.

<Reference findings>

A) As a general rule, islet related auto-antibodies such as glutamic acid decarboxylase (GAD) antibodies are negative.
B) As a general rule, ketosis should be diagnosed within 1 week; however, there are cases where it is diagnosed within 1-2 weeks.
C) Approximately 98% of all cases have an increase in blood pancreatic exocrine enzymes (such as amylase, lipase, elastase 1) at time of onset.
D) Upper respiratory tract symptoms (such as pyrexia or pharyngodynia) and gastrointestinal symptoms (such as upper abdominal pain, nausea, and vomiting) are confirmed as precursory symptoms in approximately 70% of all cases.
E) There have been cases where disease onset was in association with pregnancy.
F) The relationship with HLA DRB 1*04:05-DQB1*04:01 has been made apparent.

3. Incidence of Type 1 Diabetes Mellitus (Including Fulminant Type 1 Diabetes Mellitus)

From initial marketing to February 2016, the marketing authorization holder (MAH) estimates that there have been 3 483 patients prescribed this drug. Given that the additional indication for “unresectable advanced/recurrent non-small cell lung cancer” was approved in December 2015 and that this drug is no longer regarded a target for DPC since February 2016, the number of patients using this drug is anticipated to increase with the additional approval of dosage and administration for “radical unresectable malignant melanoma” and expansion of target to include chemotherapy naïve patients.

From initial approval to November 2015 when the package insert was revised, a total of 5 cases of adverse drug reactions (ADR) associated with type 1 diabetes mellitus have been reported including those for which the causal relationship was unknown. Of these 5 cases, the causal relationship to the product could not be ruled out for 4 cases. While incidence has not increased after this with the increasing number of patients prescribe this drug, 4 cases have been reported by February 29, 2016 (including those for which the causal relationship is unknown due to lack of information, etc.); therefore, a total of 9 cases have been reported (of which none have had fatal outcomes).

4. Revision of the Precautions Section in the Package Insert (Revised November 24, 2015)

In the Clinically significant adverse reaction subsection of the Adverse reaction section, the following text should be added (underlined parts are revised):

<u>Type 1 diabetes mellitus:</u>
<u>Type 1 diabetes mellitus (including fulminant type 1 diabetes mellitus) may occur and cause diabetic ketoacidosis. Patients should be carefully monitored for symptoms such as thirst, nausea, and vomiting or increase in blood glucose levels. If type 1 diabetes mellitus is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of insulin products should be adopted.</u>

5. Notifications from Related Medical Societies

The Japanese Society of Medical Oncology (JSMO) released a statement for proper use of nivolumab (genetical recombination), an anti-PD-1 (programmed cell death-1) antibody, dated January 21, 2016 in order to prevent future increase in incidence of various side effects

including type 1 diabetes mellitus . In addition, the director of the JSMO together with the director of the JDS released a cautionary warning on January 29, 2016 regarding onset of fulminant type 1 diabetes mellitus related to use of immune checkpoint inhibitors.

6. Case Summaries

Case 1

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
1	Female 70s	Malignant melanoma (None)	Administered 2 mg/kg every 3 weeks for 6 cycles	**Fulminant type 1 diabetes mellitus, diabetic ketoacidosis** 16 months before administration: Onset of malignant melanoma in the nasal cavity. 11 months before administration: The patient was administered immunotherapy (pulsed dendritic cell therapy) for multiple systemic metastasis. 4 months before administration: Radiation therapy was conducted for the primary tumor in the nasal cavity. Day 1 of administration: Treatment with nivolumab was initiated for malignant melanoma (Stage IV). Prior to treatment initiation with nivolumab, metastasis could be found in the lungs, liver, lymph nodes, skin, systemic subcutatneous, and adrenal glands. The patient had no history or complications related to auto-immune disease. The patient also had no history of diabetes mellitus. Day 21 of administration: Nivolumab was administered for the second time. Reduction of multiple metastases to skin and subcutaneous was confirmed. Day 63 of administration: Computed tomography (CT) scans confirm marked reduction/elimination of lung, adrenal glands, lymph nodes, skin, and subcutaneous metastatic lesions. Nivolumab was administered for the fourth time. Day 105 of administration: Nivolumab was administered for the sixth time. Hyperglycaemia was not confirmed. Day 112 of administration: Onset of thirst, impaired appetite, and malaise. Day 121 of administration: Strong emergence of thirst, nausea, vomiting, and malaise, which lead the patient to consult a nearby physician. The patient had been suffering from impaired appetite from approximately 3 days before, and was only consuming fluids. Hyperglycaemia and marked ketoacidosis was observed, and the patient was urgently admitted to the hospital. The patient was diagnosed as fulminant type 1 diabetes, and treatment using continuous administration of insulin (48 units/day) and fluid replacement (with saline solution) was initiated.

				Day 122 of administration: Ketoacidosis was resolving. Blood glucose levels were controlled so that it was maintained at 200 mg/dL. Day 123 of administration: The patient began ingesting solids. Treatment using fluid replacement was completed. Insulin treatment was switched to insulin subcutaneous injections (sliding scales) and insulin degludec 12 units/day. Day 125 of administration: Treatment was changed to insulin lispro 4-4-4 units and insulin degludec 12 units/day, and blood glucose levels were maintained and observed at around 200 mg/dL. Day 136 of administration: The patient was discharged from the hospital. When the patient was discharged, treatment administered was insulin lispro 4-4-4 units and insulin degludec 4 units/day. Day 273 of administration: Treatment was changed to insulin lispro 6-6-6 units and insulin degludec 8 units/day. Follow-up on blood glucose levels maintained at around 200 mg/dL.

Laboratory examination

	Day 105 after administration	Day 121 after administration	Day 122 after administration	Day 123 after administration	Day 207 after administration	Day 222 after administration	Day 302 after administration
Blood glucose (mg/dL)	82	571	−	−	291	−	225
HbA1c (%)	−	8.0	−	−	10.9	9.9	7.9
Blood C peptide (ng/dL)	−	−	−	<0.1	−	<0.1	−
Urine C peptide (μg/day)	−	−	−	<0.6	−	−	−
Urinary sugar	(-)	(4+)	−	−	(3+)	−	−
Urine ketone	−	(3+)	−	−	(-)	−	−
Na (mEq/L)	−	136	135	−	139	−	−
K (mEq/L)	−	5.4	5.54	−	4.4	−	−
Cl (mEq/L)	−	96	108	−	104	−	−
pH	−	7.1	7.418	−	−	−	−
BE (mmol/L)	−	-22.8	-4.3	−	−	−	−

<Laboratory tests related to auto-antibodies>
All of the following laboratory tests related to auto-antibodies tested negative and normal.
- Islet related auto-antibodies: Anti-GAD antibodies, insulin auto-antibodies
- Antinuclear antibodies: Anti-DNA antibodies, anti-ss-DNA antibodies, anti-ds-DNA antibodies, anti-RNP antibodies, anti-Sm antibodies, anti-Scl-70 antibodies, anti-Jo-1 antibodies, anti-SS-A antibodies, anti-SS-B antibodies
- Other auto-antibodies: Anti-CL-β2GPI complex antibodies, PR3-ANCA (C-ANCA)
- Serum complement: CH50, C3, C4

Concomitant medications: None

Case 2

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Primary disease (complications)		Clinical course and therapeutic measures
2	Female 60s	Malignant melanoma (Reflux oesophagitis, pollinosis)	Administered 2 mg/kg every 3 weeks for 10 cycles	**Fulminant type 1 diabetes mellitus** 5 months before administration: Onset of malignant melanoma (primary site: vagina). 1 month before administration: Resection of malignant melanoma was conducted. Day 1 of administration: Treatment with nivolumab was initiated for malignant melanoma. The patient had no history or complications related to auto-immune disease. The patient also had no history of diabetes mellitus. Day 118 of administration: Nivolumab was administered for the sixth time. Impaired appetite and hyperglycaemia (387 mg/dL) was confirmed. Day 121 of administration: The patient came for an emergency consult due to light-headed feeling and queasy. Based on the diagnosis criteria and the fact that the patient had diabetic ketoacidosis, the patient was diagnosed with fulminant type 1 diabetes mellitus. After administering saline solution, glucose-acetated Ringer's solution was administered. Treatment with intravenous human insulin (4U) and human insulin continuous infusion (2U/H) was initiated. Day 122 of administration: Administration of insulin glargine (12U) and insulin aspart (4-4-4-0) was initiated. After treatment initiation, the patient was referred to a diabetologist for a consult on blood glucose control. Day 123 of administration: The patient did not complain of dysphoria or vertigo, etc. Continuous infusion of human insulin was completed on the same day. After this procedure, the patient's blood glucose was controlled by an insulin injection in the morning, at lunch, in the evening, and before bedtime. Hyperglycaemia was resolving. Day 126 of administration: Abdominal echo was conducted. There were no obvious findings to suggest pancreatic lesions. Day 127 of administration: Blood C peptide levels were 0.06 ng/mL, and the patient tested negative for GAD antibodies. Day 129 of administration: The patient did not respond to the glucagon stimulation test. Day 139 of administration: Nivolumab was administered for the seventh time. Blood glucose levels were within the acceptable baseline. Day 206 of administration: Nivolumab was administered for the tenth time. Type 1 diabetes mellitus was not resolved.

Laboratory examination

	1 day before administration	Day 118 of administration	Day 121 of administration	Day 122 of administration	Day 123 of administration	Day 127 of administration	Day 193 of administration
HbA1c (%)	-	-	7.6	-	-	-	6.6
Blood glucose (mg/dL)	232	387	531	165	190	-	204
Urinary sugar	-	-	(4+)	-	-	-	-
Urine ketone	-	-	(3+)	(-)	-	-	-
Blood C peptide (ng/mL)	-	-	-	-	-	0.06	-
Venous blood gas pH			7.144	7.296			

<Laboratory tests related to auto-antibodies>
• GAD antibodies: Negative

Concomitant medications: beclometasone dipropionate, ursodeoxycholic acid, butyric acid bacteria product, carbazochrome sodium sulfonate hydrate, tranexamic acid, killed escherichia coli/hydrocortisone

[References]

1. Notification regarding fulminant type 1 diabetes mellitus during use of nivolumab (genetical recombination) (Notification No. 0128-1 to 0128-3 from the Safety Division of the Pharmaceutical and Environmental Health Bureau (PEHB) dated January 28, 2016)
2. Pharmaceuticals and Medical Devices Agency (PMDA): Notification for revision of precautions (pharmaceuticals) https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0001.html
3. JSMO: Regarding proper use of nivolumab (Opdivo®), an anti-PD-1 antibody http://www.jsmo.or.jp/ (Only available in the Japanese language)
4. JSMO and JDS: Regarding onset of fulminant type 1 diabetes mellitus related to use of immune checkpoint inhibitors http://www.jsmo.or.jp/ http://www.jds.or.jp/modules/important/index.php?page=article&storyid=58 (Only available in the Japanese language)
5. JDS: Investigative research committee on etiological diagnosis, pathology, and treatment of type 1 diabetes in Japanese patients – Subcommittee on fulminant and acute onset type 1 diabetes http://www.jds.or.jp/modules/study/index.php?content_id=4 (Only available in the Japanese language)
6. Websites related to Ono Pharmaceutical Co., Ltd. and Bristol-Myers K.K.: Opdivo.jp https://www.opdivo.jp/contents/ (Only available in the Japanese language)

2

Change in Report Forms for "Drugs and Medical Devices Safety Information Reporting System"

1. System Overview

PMDA has elicited the cooperation of all healthcare professionals in medical institutions, pharmacies, etc. to report information related to ADR, infections or malfunctions for drugs, medical devices, and/or regenerative medical products as part of the Drugs and Medical Devices Safety Information Reporting System (hereinafter referred to as the "Safety Information Reporting System")[1]. This system is in accordance with the laws related to quality, efficacy, and safety assurance of pharmaceuticals, medical devices, etc. Article 68, Version 10 Section 2* (Act No. 145 of 1960. Hereinafter referred to as the "Drugs and Medical Devices Act").

The reported information is analyzed and evaluated from an expert perspective, and is utilized as the basis for implementing necessary safety measures and is useful in ensuring post-marketing safety measures for drugs, medical devices and regenerative medical products such as through information provision to a wide range of healthcare professionals.

*Drugs and Medical Devices Act Article 68, Version 10 Section 2

Pharmacy proprietors, proprietors of hospitals, clinics, or medical facilities for domesticated animal as well as physicians, dentists, pharmacists, MAHs, veterinarians, and any other healthcare professionals are required to report any occurrences of ADRs, diseases, disorders, or deaths as well as infections either due to or suspected to be due to use of relevant pharmaceuticals, medical devices and/or regenerative medical products to the MHLW if it is deemed necessary since these occurrences will result in or increase public health hazards.

2. Change in Contents of the Report Forms

The Drugs Safety Information Report Form was revised so that extra description columns and explanations for what should be included in the columns were added to the unclear parts of the mentioned contents[1]. In addition, the Quasi-Drugs/Cosmetics Safety Information Report Form was revised in a similar manner so that the necessary description updates were included. Furthermore, the Medical Devices Safety Information Report Form and Regenerative Medical Products Safety Information Report Form were revised accordingly with description updates.

(Changes in the Drugs Safety Information Report Form)

- "Age of ADR onset"
  Changed the form so that postnatal age of infants can be entered as month/week-old units.
- "Seriousness of ADR, etc."
  The form is now easier to understand because it includes "Assessment criteria for seriousness".
- "Suspected drug(s)"
  In order to clearly differentiate "suspected drug(s)" from "concomitant medications" which were used at the time of ADR onset but are not suspected to have a causal relationship

with the ADR, it is now easier to understand which drugs should be included in the entry column for “suspected drug(s)”.
In addition, as PMDA would like healthcare professionals to circle the most likely suspected drug(s), the form now clearly includes a cautionary note regarding circling the relevant product(s) and where this circle should be noted.

- “Reason for use”
  As PMDA would like healthcare professionals to indicate what type of disease and/or symptoms the drug(s) were used for, the form now includes additional comments regarding “disease name, symptom name”.
- Indicating vaccine lot
  Since lot numbers are important information when deliberating safety measures, a new entry column for vaccine lots was included on the form.
- “Laboratory test values”
  Since laboratory test values prior to administration, on the day of ADR onset, and on the day of outcomes is necessary, the form now includes a cautionary note that indicates these laboratory test values should be included.

3. Requests

By having healthcare professionals report ADR, etc. directly to PMDA, the Safety Information Reporting System allows for prompt gathering of occurrences of such ADR events, etc. and is important to use in conjunction with information reported through companies so that proper safety measures can be implemented. Furthermore, the PMDA is currently requesting all healthcare professionals to directly report information regarding ADR, etc. not only for drugs but for quasi-drugs/cosmetics, medical devices, and regenerative medical products. Your continued cooperation is greatly appreciated.

1. “Revisions in practices of reporting ADR, infections, and malfunctions from medical institutions, etc. regarding drugs, medical devices, or regenerative medical products”
   (PSEHB Notification No. 0325-4 of the Phramaceutical Safety and Environmental Health Bureau , MHLW, dated March 25, 2016)

<Reference>

- Reporting ADR, infections, or malfunctions in accordance with the Drugs and Medical Devices Act (for healthcare professionals)
  http://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html (Only available in the Japanese language)

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated March 22, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Furosemide

Brand name (name of company)	Lasix Tablets 10 mg, 20 mg, and 40 mg, Lasix Fine Granules 4% (Sanofi K.K.), and the others Lasix Injection 20 mg (Sanofi K.K.), and the others Lasix Injection 100 mg (Sanofi K.K.), and the others Eutensin Capsules 40 mg (Sanofi K.K.)
Therapeutic category	Diuretics
Indications	1. Hypertension (including essential and renal hypertension, etc.), malignant hypertension, cardiac-induced edema (congestive cardiac failure), renal-induced edema, hepatic-induced edema, pre-menstrual tension, edema due to peripheral vascular disorders, stimulating excretion of urinary calculus 2. Hypertension (including essential and renal hypertension, etc.), malignant hypertension, cardiac-induced edema (congestive cardiac failure), renal-induced edema, hepatic-induced edema, brain edema, stimulating excretion of urinary calculus 3. Oliguria due to acute or chronic renal failure 4. Essential hypertension

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Interstitial pneumonia:** Interstitial pneumonia may occur. If cough, dyspnea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations such as chest X-rays and chest CT scans 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 reaction (for which a causal relationship to the product could not be ruled out) for the past 3 years and 5 months (from April 2012 to August 2015). Cases of interstitial pneumonia: 2 cases (no fatal case) The number of patients using this drug estimated by the MAH: Approximately 930 000 (from July 2014 to June 2015) Launched in Japan: May 1965

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Chronic cardiac failure (None)	Unknown dosage administered for 899 days ↓ 20 mg administered for 61 days	**Interstitial Pneumonia** Day 1 of administration: Treatment with furosemide was initiated. Day 896 of administration: The patient consulted the hospital due to acute pneumonia. Day 899 of administration: The patient was admitted to the hospital for treatment since medical conditions were not resolving. Combination therapy with cefotiam hydrochloride and amikacin sulfate was administered but conditions did not resolve. Day 901 of administration: Suspected diagnosis of the patient was determined to be interstitial pneumonia (assumed that antibiotics were the cause). Methylprednisolone 125 mg DIV was administered for 4 days after which the patient was maintained on prednisolone 30 mg/day as symptoms were resolving. Day 903 of administration: The patient was discharged from the hospital after recovering (oral administration with prednisolone 30 mg/day was continued). Day 923 of administration: Dosage of prednisolone was decreased to 20 mg/day and symptoms did not worsen. Day 960 of administration (Day of discontinuation): The patient was admitted to the hospital due to exacerbated dyspnea. Definite honeycomb structures were confirmed based on imaging diagnostics (chest CT); thus, the patient was diagnosed with interstitial pneumonia. Administration of furosemide was discontinued. Treatment with oxygen inhalation and pulse therapy (methylprednisolone 500 mg×2 DIV) were reinitiated, and the patient showed an effective response. 1 day after discontinuation: Drug lymphocyte stimulation tests (DLST) were conducted. The patient tested positive for furosemide (S.I. 2.5) but negative for pilsicainide hydrochloride hydrate (S.I. 0.9). 11 days after discontinuation: The patient tested negative for furosemide (S.I. 0.9) on the DLST conducted. 13 days after discontinuation: The patient had pyrexia at 40°C, and was transferred to a different hospital due to poor clinical condition. 16 days after discontinuation: The patient died due to multiple cerebral hemorrhages.

Laboratory examination

Name of laboratory tests	Day 899 of administration	Day 901 of administration	Day 906 of administration	Day 911 of administration	Day 918 of administration	Day 922 of administration	Day 942 of administration	Day 955 of administration	Day 960 of administration (Day of discontinuation)	1 day after discontinuation	8 days after discontinuation	11 days after discontinuation	14 days after discontinuation
WBC count (/μL)	5610	6570	7590	6700	5630	5590	8600	8440	5940	6280	7630	5250	15870
Neutrophil (%)	68.5	65.7	80.8	73.4	-	64.7	84.4	-	79.8	78.1	83.6	-	-
Eosinophil (%)	4.5	5.2	0.0	0.0	-	1.1	0.0	-	1.0	0.5	0.0	-	-
Lymphocyte (%)	18.2	20.9	14.6	20.4	-	28.3	12.8	-	16.0	18.2	10.4	-	-
CRP (mg/dL)	6.62	6.52	0.89	0.25	0.04	0.02	0.09	4.60	7.85	14.62	1.53	0.81	4.97
LDH (IU/L)	430	-	346	-	388	391	604	592	543	729	585	-	-
KL-6 (U/mL)	600	-	-	983	859	-	685	-	-	780	-	-	834

Concomitant medications: aspirin, warfarin potassium, benidipine hydrochloride, magnesium oxide, acetoaminophen, pilsicainide hydrochloride hydrate

4

Revision of Precautions (No. 273)

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 March 22 and 23, 2016.

1

Hypnotics and sedatives, anxiolytics

Flunitrazepam (injections)

Brand name	Rohypnol Intravenous Injections 2 mg (Chugai Pharmaceutical Co., Ltd.), Silece Intravenous Injections 2 mg (Eisai Co., Ltd.)
Important Precautions	Depth of anesthesia and sedation should be limited to the minimum depth required for the management of surgery or laboratory test. Prior to administration of this drug, artificial ventilation devices such as oxygen inhalers, suction instruments, and trachea intubation sets as well as emergency analeptic drugs such as vasopressors should be prepared. In addition, flumazenil (benzodiazepine receptor antagonist) should be prepared as necessary. Respiratory and cardiac function should be carefully monitored while being mindful of the respiratory tract during treatment with this drug. The patient's cardiorespiratory dynamics should be continuously monitored using devices such as a pulse oximeter or sphygmomanometer.
Adverse reaction (clinically significant adverse reaction)	**Apnoea, respiratory depression, and glossoptosis:** Apnoea, respiratory depression, or glossoptosis may occur and may lead to serious outcomes. Patients should be carefully monitored. If these symptoms are observed, the airway should be opened and appropriate measures such as artificial respiration should be adopted. **Confusional state:** Confusional state may occur.

2

Antipyretics and analgesics, anti-inflammatory agents

Loxoprofen sodium hydrate (for oral use)

Brand name	Loxonin Tablets 60 mg, Loxonin Fine Granules 10% (Daiichi Sankyo Co., Ltd.), Loxoprofen Sodium Oral Solution 60 mg (Nichi-Iko Co., Ltd.), and the others
Adverse reaction (clinically significant adverse reaction)	**Stenosis and obstruction of small intestine and large intestine:** Stenosis or obstruction of small intestine or large intestine may occur in association with small intestine or large intestine ulcers. Patients should be carefully monitored. If any symptoms such as nausea and vomiting, abdominal pain, and abdominal distension are observed, administration of this drug should be discontinued immediately and appropriate measures should be adopted.

3

Psychotropics

Paliperidone palmitate

Brand name	Xeplion Aqueous Suspension for IM Injection 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg (Janssen Pharmaceutical K.K.)
Adverse reaction (clinically significant adverse reaction)	**Anaphylaxis:** Anaphylaxis 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. Furthermore, cases of anaphylaxis have been reported in patients who have previously tolerated oral paliperidone or oral risperidone.

4

Psychotropics

Risperidone (Injections)

Brand name	Risperdal Consta Intramuscular Injection 25 mg, 37.5 mg, and 50 mg (Janssen Pharmaceutical K.K.)
Adverse reaction (clinically significant adverse reaction)	**Anaphylaxis:** Anaphylaxis 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. Furthermore, cases of anaphylaxis have been reported in patients who have previously tolerated oral risperidone.

5

Ophthalmic agents

Verteporfin

Brand name	Visudyne Injection 15 mg (Novartis Pharma K.K.)
Adverse reaction (clinically significant adverse reaction)	**Convulsions**

6

Urogenital and anal organ agents – Miscellaneous

Mirabegron

Brand name	Betanis Tablets 25 mg and 50 mg (Astellas Pharma Inc.)
Important Precautions	This drug may increase blood pressure. Blood pressure should be measured periodically before and during treatment with this drug.
Adverse reaction (clinically significant adverse reaction)	**Hypertension:** Mirabegron may increase blood pressure. Cases of systolic blood pressure greater than or equal to 180 mmHg or diastolic blood pressure greater than or equal to 110 mmHg have been reported with this drug. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

7

Antipyretics and analgesics, anti-inflammatory agents

Products containing loxoprofen sodium hydrate (OTC drugs for oral use)

Brand name

Loxonin S (Daiichi Sankyo Healthcare Co., Ltd.), and the others

Consultation

If the following symptoms are observed after taking this drug, immediately discontinue use of this drug as these may be adverse reactions, and show this document to your physician or pharmacist for consultation.

Occurrence of peptic ulcers or oedema after administration of the drug

In addition, severe symptoms such as gastrointestinal haemorrhage (associated with symptoms such as haematemesis, nausea and vomiting, abdominal pain, black tar-like stool, and bloody stool), gastrointestinal perforation (indicates a hole in the gastrointestinal area, and associated with symptoms such as nausea and vomiting and severe abdominal pain), and stenosis or obstruction of small intestine or large intestine (associated with symptoms such as nausea and vomiting, abdominal pain, and abdominal distension) may rarely occur. In such cases, immediately seek medical attention.

8

Miscellaneous metabolism agents

Mycophenolate mofetil

Brand name

Cellcept Capsules 250, Cellcept Powder for Oral Suspension 31.8% (Chugai Pharmaceutical Co., Ltd.), and the others

Warning

This drug has demonstrated teratogenic effects in humans. Women of reproductive potential must undergo pregnancy testing before administration of this drug, and treatment can only be initiated after confirming negative test results. In addition, prior to initiating treatment up until 6 weeks after stopping treatment with this drug, patients must utilize reliable contraception methods and also be periodically checked by consultations and repeated pregnancy tests, etc. to ensure that no pregnancy occurs.

Relative Contraindications

~~Women of reproductive potential~~ (deleted)

Important Precautions

This drug has teratogenic effects; therefore, women of reproductive potential must be made aware of the following cautionary points before use.

1. This drug has been reported to cause teratogenicity.
2. Pregnancy tests must be conducted prior to initiating treatment with this drug and test results must be negative.
3. Contraception must be utilized before, during and for 6 weeks after stopping treatment with this drug.
4. Patients should be periodically checked by consultations and repeated pregnancy tests, etc. to ensure that no pregnancy occurs during the administration of this drug. If pregnancy is suspected, the patient should immediately contact the doctor in charge.

Use in Pregnant, Parturient and Nursing Women

(1) This drug should not be administered to pregnant women or women suspected of being pregnant. [Teratogenicity including those of the ears (external auditory canal atresia, microtia, etc.), eyes (coloboma, microphthalmos, etc.), face (hypertelorism of the orbits, micrognathia, etc.), fingers (syndactyly, polydactyly, brachydactyly, etc.), heart (atrial and ventricular septal defect, etc.), esophagus (esophageal atresia, etc.), and nervous system (spina bifida, etc.) have been reported among patients taking this drug during pregnancy. Abortions have been reported in 45 to 49% of pregnant women exposed to this drug. Furthermore, in teratology studies, exencephaly, gastroschisis, etc. in rats (at 6 mg/kg/day), and patent ductus arteriosus, thoracoschisis, gastroschisis, etc. in rabbits (at 90 mg/kg/day) have been reported.]

	(2) ~~As a general rule, this drug should not be administered to women of reproductive potential; however, if administration is absolutely necessary, the drug should only be administered if it is determined that treatment benefits outweigh the associated risks.~~ (deleted)

5

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of March 31, 2016)

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

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg [*1]	Shionogi & Co., Ltd.	March 18, 2016
	Eribulin Mesilate Halaven Intravenous Injection 1 mg[*2]	Eisai Co., Ltd.	February 29, 2016
	Risperidone Risperdal Tablets, 1 mg, 2 mg, Fine Granules 1 %, Risperdal OD Tablets 0.5 mg 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL [*3]	Janssen Pharmaceutical K.K.	February 29, 2016
	Rituximab (Genetical Recombination) Rituxan Injection 10 mg/mL[*4]	Zenyaku Kogyo Co., Ltd.	February 29, 2016
	Progesterone Utrogestan vaginal capsules 200mg	Fuji Pharma Co., Ltd.	February 18, 2016
	Indium pentetreotide (^{111}In) OctreoScan Kit for Intravenous Use	FUJIFILM RI Pharma Co., Ltd.	January 27, 2016
	Esflurbiprofen/Mentha oil Loqoa Tape	Taisho Pharmaceuticals Co., Ltd.	January 21, 2016
	Bosentan hydrate Tracleer 32 mg dispersible tablets for pediatrics	Actelion Pharmaceuticals Japan Ltd.	January 12, 2016
	Ozenoxacin Zebiax Lotion 2%	Maruho Co., Ltd.	January 7, 2016
	Vandetanib Caprelsa Tablets 100 mg	AstraZeneca K.K.	December 24, 2015
	infliximab (genetical recombination) Remicade Intravenous Infusions 100 mg[*5]	Mitsubishi Tanabe Pharma Corporation	December 21, 2015
	Apixaban Eliquis Tablets 2.5 mg, 5 mg[*6]	Bristol-Myers K.K.	December 21, 2015
	nivolumab (genetical recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*7]	Ono Pharmaceutical Co., Ltd.	December 17, 2015
	leuprorelin acetate Leuplin PRO Injections Kit 22.5 mg	Takeda Pharmaceutical Co., Ltd.	December 15, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
absorbed diphtheria-purified pertussis-tetanus-inactivated polio (salk vaccine) combined vaccine Square Kids Subcutaneous Injections Syringe	Kitasato Daiichi Sankyo Vaccine Co., Ltd.	December 9, 2015
venlafaxine hydrochloride Effexor SR Capsules 37.5 mg, 75 mg	Pfizer Japan Inc.	December 8, 2015
Trabectedin Yondelis Intravenous Infusions 0.25 mg, 1 mg	Taiho Pharmaceutical Co., Ltd.	December 7, 2015
Rivaroxaban Xarelto Fine Granules 10 mg, 15 mg*8	Bayer Yakuhin, Ltd.	December 7, 2015
None Miticure House Dust Mite Sublingual Tablets 3,300 JAU, 10,000 JAU	Torii Pharmaceutical Co., Ltd.	December 3, 2015
tiotropium bromide hydrate Spiolto Respimat 28 puffs	Nippon Boehringer Ingelheim Co., Ltd.	December 3, 2015
Lusutrombopag Mulpleta Tablets 3 mg	Shionogi & Co., Ltd.	December 1, 2015
Levetiracetam E Keppra Intravenous Infusions 500 mg	UCB Japan Co., Ltd.	December 1, 2015
insulin degludec (genetical recombination) / insulin aspart (genetical recombination) Ryzodeg FlexTouch	Novo Nordisk Pharma Ltd.	December 1, 2015
sucroferric oxyhydroxide P-TOL Chewable Tablets 250 mg, 500 mg	Kissei Pharmaceutical Co., Ltd.	November 27, 2015
ombitasvir hydrate/paritaprevir hydrate/ritonavir Viekirax Combination Tablets	AbbVie G.K.	November 26, 2015
glatiramer acetate Copaxone S.C. Injections 20 mg Syringe	Takeda Pharmaceutical Co., Ltd.	November 26, 2015
vildagliptin/metformin hydrochloride EquMet Combination Tablets LD and HD	Novartis Pharma K.K.	November 26, 2015
Omarigliptin Marizev Tablets 12.5 mg, 25 mg	MSD K.K.	November 26, 2015
None Actair House Dust Mite Sublingual Tablets 100 units (IR) and 300 units (IR)	Shionogi & Co., Ltd.	November 19, 2015
Rivaroxaban Xarelto Tablets 10 mg, 15 mg*8	Bayer Yakuhin, Ltd.	September 24, 2015

*1 Pain associated with chronic lumbago
*2 Malignant soft tissue sarcoma
*3 Irritability associated with autism spectrum disorder in childhood
*4 Prophylaxis of antibody-related type rejection in the ABO blood group incompatibility transplant of kidney and liver transplants
*5 Acute stage of Kawasaki's disease
*6 Treatment of venous thromboembolism [deep vein thrombosis (DVT) and pulmonary embolism (PE)], and prophylaxis of recurrent DVT and PE
*7 Unresectable advanced/recurrent non-small cell lung cancer
*8 Treatment of DVT and PE, and prophylaxis of recurrent DVT and PE