Pharmaceuticals and Medical Devices Safety Information

No. 327 October 2015

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

Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 327 October 2015

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

[Outline of Information]

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

Reporting of safety information such as adverse 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 reactions
AG	Anion gap
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BE	Base excess
BUN	Blood urea nitrogen
CHDF	Continuous hemodiafiltration
CK	Creatine kinase
CPK	Creatine phosphokinase
CRE	Creatinine
CRP	C-reactive protein
CT	Computed tomography
DIC	Disseminated intravascular coagulation
DIHS	Drug-induced hypersensitivity syndrome
ELD	Evaluation and Licensing Division
EPPV	Early Post-marketing Phase Vigilance
FT3	Free triiodothyronine
FT4	Free thyroxine
GAD	General Affairs Division
Hb	Hemoglobin
HCO_3	Bicarbonate ion
HPB	Health Policy Bureau
ILD	Interstitial lung disease
JCQHC	Japan Council for Quality Health Care
JCS	Japan Coma Scale
K	Potassium
KCl	Potassium chloride
KI	Potassium iodide
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
Na	Sodium
OMDE	Office of Medical Devices Evaluation
PAM-Cl	Pralidoxime chloride
PAM-I	Pralidoxime iodide
PCT	Procalcitonin
PFSB	Pharmaceutical and Food Safety Bureau
Plt	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PMX	Polymyxin B-immobilized fiber
PTP	Press Through Packages
SD	Safety Division
SMBG	Self-monitoring blood glucose
SpO_2	Oxygen saturation
TPO	Thyroperoxidase

UA	Uric acid
WBC	White blood cells

1

Utilization of Blood Glucose Meters, etc. that Use Enzymatic Electrodes

1. Introduction

Revisions of the precautions for medical devices or in vitro diagnostics to measure blood glucose levels, such as glucose analyzers and glucose assay kits for blood tests (hereinafter referred to as “blood glucose meters”), have been advised by the Ministry of Health, Labour and Welfare (MHLW)[*1]. These revisions are in regards to false high values of blood glucose levels measured in patients being administered pralidoxime iodide (PAM-I).

*1: Pharmaceutical and Food Safety Bureau (PFSB) / Safety Division (SD) Notification No. 0907001 “Regarding Instructions on Revisions of the “Precautions” in the Package Insert of Blood Glucose Meters” dated September 7, 2007
PFSB/SD Notification No. 0907003 “Regarding Revisions of the “Precautions” in the Package Inserts” dated September 7, 2007

Based on recent findings, blood glucose meters using enzymatic electrodes as a measurement principle are influenced by serum iodide ion concentration. In addition, there was a case report of false high values of blood glucose suggesting a contamination of residual iodine antiseptics on the patient’s skin when collecting blood. Therefore, the precautions in the package insert were revised in order to give the alert regarding blood collection methods, etc. The following presents the details of these revisions.

2. Regarding Blood Glucose Meters, etc.

Blood glucose levels are measured using a combination of blood glucose reagents and blood glucose meters. Blood glucose reagents include glucose assay kits for blood tests and glucose assay kits for self-monitoring; blood glucose meters include self-monitoring blood glucose (SMBG) meters, glucose analyzers, and automated analyzers. Furthermore, the measurement principles of such analysis can be broadly divided into assays using enzymatic electrodes and enzyme colorimetric assays[*2].

*2: Assays using enzymatic electrodes: Method of measurement that allows specific enzymes to react with glucose present in the blood and calculates the electrical current when a voltage is applied to the reactant.
Enzyme colorimetric assays: Method of measurement that allows specific enzymes to react with glucose present in the blood and calculates the color of the reactant.

3. Recently Identified Incidents, etc.

The research study showed that the measured glucose levels increased depending on the concentration of PAM-I added to the blood samples when glucose levels were measured with blood glucose meters using enzymatic electrodes. A similar result was also seen when potassium iodide (KI) was added to blood samples. On the other hand, adding pralidoxime

chloride (PAM-Cl) or potassium chloride (KCl) to blood samples did not affect the measured glucose levels.

For cases using enzyme colorimetric assays, glucose levels varied when PAM-I or PAM-Cl was added to blood samples due to the influence of PAM salts on the measured levels at wavelength bands utilized for measurements. However, such influences were not seen for blood samples added with KI or KCl.

Based on the above, there is a possibility that results of blood glucose meters using enzymatic electrodes may be influenced by iodide ions[1].

In addition, there was a case report (December 2015) of false high values of blood glucose measured using a blood glucose meter with enzymatic electrodes suggesting a contamination of residual iodine antiseptics on the patient's skin when collecting blood. Based on the PMDA's investigation results, there were reports of increased blood iodine concentration due to use of iodine antiseptics in burn patients[2, 3].

Given these various reports, the MHLW has notified manufacturers of blood glucose meters, etc. to revise the precautions in package inserts and to provide relevant information to medical institutions. This notification, "Revision of the Precautions in the Package Insert of Medical Devices and In Vitro Diagnostics for Blood Glucose Measurements Using Enzymatic Electrodes" (PFSB/ Evaluation and Licensing Division (ELD) / Office of Medical Devices Evaluation (OMDE) Notification No. 0721-2 and PFSB/SD Notification No. 0721-2 dated July 21, 2015), was issued to give the alert regarding blood collection methods, etc.

<Details of Revisions>

1. In the "Important Precautions" section in the Precautions of the package inserts of glucose analyzers and SMBG meters that use enzymatic electrodes, the following text should be added:
   Avoid collecting blood from sites using topical preparations that include iodine. (It may cause false high values.)
2. In the "Important Precautions" section in the Precautions of the package inserts of automated analyzers, etc. that use enzymatic electrodes to measure blood glucose, the following text should be added:
   Avoid collecting blood from sites using topical preparations that include iodine when measuring blood glucose. (It may cause false high values.)
3. In the "Operating Precautions" of the package inserts of in vitro diagnostics used when enzymatic electrodes are used to measure blood glucose, the following text should be added as an interfering substance:
   If there is a substance that releases iodide ions in the measured sample, it may result in false high values.

4. Requests for Healthcare Professionals

Please avoid collecting blood from sites using topical preparations that include iodine, and please be aware that false high values may occur if the measured sample contains a substance that releases iodide ions.

<References >

1. Nagase S, et al. (2013). Interference by Pralidoxime (PAM) salts in clinical laboratory tests. *Clinica Chimica Acta*. 416, 72-79.
2. John L, et al. (1980). A Critical Evaluation of Povidone-iodine Absorption in Thermally Injured Patients. *The Journal of Trauma*. 20 (2), 127-129.
3. John P., Jonathan L.M. (1976). Complications of Povidone-iodine Absorption in Topically Treated Burn Patients. *The Lancet*. Feb.7, 280-282.

2

Precautions Concerning Recurrent and Similar Incidents of Medical Accidents

1. Introduction

The MHLW and Pharmaceuticals and Medical Devices Agency (PMDA) are analyzing information on medical accidents and near-miss events collected as a part of the Project to Collect Medical Near-Miss/Adverse Event Information and the Project to Collect and Analyze Pharmaceutical Near-Miss Events run by the Japan Council for Quality Health Care (JCQHC). The MHLW and PMDA also strive to caution healthcare professionals by issuing notifications on the prevention of medical accidents related to pharmaceuticals and medical devices and by preparing the "PMDA Medical Safety Information."

However, as a result of recent analysis of cases reported to the JCQHC between July 1 and December 31, 2014, the occurrence of following events that had been cautioned in the notifications or "PMDA Medical Safety Information" was confirmed.

Therefore, in addition to detailing confirmed recurrent incidents, this section will especially focus on "Accidental ingestion of Press Through Packages (PTP) sheet" and "Error in dosage unit of insulin administered."

2. Major Recurrent Incidents

(1) Accidental ingestion of PTP sheet

- Incident report

  An elderly patient accidentally ingested oral drugs with the PTP sheet still intact. The underlying cause for this was that, although the patient was supposed to be supervised when taking medication, supervision was not provided due to a busy schedule by staff members.

- Preventative measures for recurrence adopted by the facility where the incident occurred

  As precautions for preventing accidental ingestions, the facility adopted measures to provide one dose packages or strict supervision for elderly patients anticipated to have difficulty managing drug administration on their own.

- Related notifications or precautions

  - Joint Notification of Health Policy Bureau (HPB) / General Affairs Division (GAD) No. 0915-2, PFSB/GAD Notification No. 0915-5, and PFSB/SD Notification No. 0915-1 dated September 15, 2010
    "Preventative measures for accidental ingestion of PTP sheet (request for precaution and dissemination to medical facilities and pharmacies)"
    http://www.pmda.go.jp/files/000415758.pdf (only available in the Japanese language)

Preventative Measures for Recurrence

1. In order to prevent accidental ingestion, PTP sheets have a one-direction horizontal or vertical dotted line so that the sheet cannot be divided into individual pieces. Caution should be exercised so that these sheets are not cut into individual pieces using scissors when dispensing, administering, etc.

2. The patients and family, etc. should be instructed as necessary to store the PTP sheets without cutting it into individual pieces as much as possible, and to push out the drug from the PTP sheet and ingest only the drug at the time of administration. If an odd number of drugs must be dispensed/administered and it becomes necessary to cut the sheet into individual pieces, the patients and family should be adequately instructed to be cautious about accidental ingestion of PTP sheets. In addition, caution (including providing supervision during oral administration) should be instructed to caregivers and family members, especially to those who care for elderly patients, patients who may accidentally ingest PTP sheets, and patients who are anticipated to have difficulty managing drug administration on their own.

3. If necessary, prescribing the drugs as a one dose package should be considered for elderly patients, patients who may accidentally ingest PTP sheets, and patients who are anticipated to have difficulty managing drug administration on their own. Furthermore, the pharmacy should consider whether the drugs can be dispensed as a one dose package, and should dispense it as necessary after consultation with the prescribing physician.

- National Consumer Affairs Center of Japan:
  "Beware! Accidental ingestion of medication packaging especially among the elderly." (November, 2010)
  http://www.kokusen.go.jp/e-hello/data/ncac_news22_4.pdf

Consumers Affairs Agency:
"Please be cautious about accidental ingestion by the elderly!" (September 16, 2015)
http://www.caa.go.jp/safety/pdf/150916kouhyou_1.pdf (only available in the Japanese language)

(2) Error in dosage unit of insulin administered

- Incident report

  100 units of insulin injection fluid was coinfused with parenteral infusions (10% dextrose solution) when only 10 units should have been coinfused. The underlying cause for this was that the person in charge mistakenly interpreted the label "1000 units/10 mL" on the insulin injection fluid bottle as approximately 10 units for 1 mL. Although a constant number of insulin syringes are placed in every ward of the facility, such syringes were not utilized for this case.

- Preventative measures for recurrence adopted by the facility where the incident occurred

  The facility adopted measures to conduct training regarding insulin products including information on unit conversion and use of specific syringes and to disseminate confirmation rules once again.

- Related notifications or precautions

- PMDA Medical Safety Information No. 23 "Precautions in Handing of Insulin Syringes"
  https://www.pmda.go.jp/files/000153172.pdf

Noted Incident 1

Although instructions stated to coinfuse insulin 0.1 mL to parenteral infusions, the person in charge assumed that 0.1 mL was 1 unit and coinfused 1 unit (0.01 mL) using the insulin syringe, and the patient suffered from hyperglycaemia.

Preventative Measures for Recurrence

Confirm that there are no errors in unit conversions for insulin.
(Disseminate the information that 1 mL of insulin injection fluid is 100 units)
(When preparing the medication, always confirm how many mL of insulin the instructed units is)

Noted Incident 2

When administering 4 units of insulin, the person in charge assumed that 4 units was 0.4 mL and administered 0.4 mL (40 units) using a syringe for tuberculin, and the patient suffered from hypoglycaemia.

Preventative Measures for Recurrence

Be cautious about mix-ups between insulin syringes and other syringes
("UNITS" is always indicated on insulin syringes; however, syringes for tuberculin or other general-purpose syringes do not have this indication.)

Noted Incident 3

Because the instructions stated 30 units per day, the person in charge used a 30 unit insulin syringe and measured to the maximum volume and coinfused this every day. On one particular day, the person in charge mistakenly took a 50 unit insulin syringe and measured to the maximum volume as usual and coinfused the mistaken amount.

Preventative Measures for Recurrence

Confirm the type (size) of insulin syringe used
(There are various types of insulin syringes for different units; therefore, if multiple types are utilized, review the types adopted in the facility so as to prevent mix-ups.)

(3) Other recurrent and similar incidents

(Analysis results of cases reported to the JCQHC between July 1 and December 31, 2014)
The following chart is a list of medical accident information and recurrence of near-miss accidents, etc.

[Pharmaceuticals]

No.	Content	Preventative Measures for Recurrence and Related Notifications
1	Prescription error of the total weight of the formula and weight of the active ingredient of powder	The method of the describing details of powders on the prescription is basically described as the weight of the formula contents, and drug name is described as the brand name, and, if the weight of the drug substance was exceptionally described, clearly show that it is the [amount of drug substance]. Joint Notification of HPB No. 0129-3 and PFSB Notification No. 0129-5 dated January 29, 2010, "Publication of the Expert Panel Report on Description Method of Oral Prescription Drugs (request for dissemination)" (Only available in the Japanese language) http://www.pmda.go.jp/files/000145210.pdf
2	Error in method of administering potassium formula (accidental one-shot intravenous injection)	Be aware that potassium formulae are pharmaceuticals that require particular safety control (pharmaceuticals that require caution for cardiac arrests), and recheck the label and administration method of the drug before administration. Joint Notification of HPB No. 1204001 and PFSB/SD Notification No. 1204001 dated December 4, 2010, "Strengthening and enforcing preventative measures for medical accidents due to pharmaceuticals with similar brand names (precautions)" (Only available in the Japanese language) http://www.pmda.go.jp/files/000146020.pdf PMDA Medical Safety Information No. 19 "Administration error of concentrated potassium (K) solutions for injections" http://www.pmda.go.jp/files/000153903.pdf
3	Rectal injury caused by glycerin enemas given in a standing position	Enemas should be given to a patient in the left lateral position as much as possible. (The standing position in particular puts pressure on the abdomen and makes the angle of the anterior rectal wall sharp, thereby making it easier for the tip of a tube to touch the anterior rectal wall and create a risk of perforation.) PMDA Medical Safety Information No. 34 "Precautions in Handling of Glycerin Enemas" https://www.pmda.go.jp/files/000153582.pdf

[Medical Devices]

No.	Content	Preventative Measures for Recurrence and Related Notifications
1	Metal materials were pulled with great force by MRI machines	Make sure that there are no magnetic objects before entering the magnetic resonance imaging (MRI) room. (The MRI room has a strong magnetic field at all times, and it is strictly prohibited to bring magnetic objects into the MRI room.) PMDA Medical Safety Information No. 26 “Precautions for MRI Scans (Part 2)” https://www.pmda.go.jp/files/000153828.pdf
2	Burn caused by heat from the tip of electric scalpels, etc.	In principle, do not place the tip of electric scalpels or lasers directly on a drape. Using a holster or a silicon mat could be helpful depending on the circumstances during surgery. PMDA Medical Safety Information No. 33 “Accidental Burns during Surgery” https://www.pmda.go.jp/files/000153041.pdf
3	Incorrect intubation of nasogastric tubes	After tube intubation, confirm the position of the tube by using multiple methods. (Confirmation of correct tube positioning may be difficult to determine by the whooshing sound alone.) PMDA Medical Safety Information No. 42 “Precautions in Handling of Nasogastric Tubes” https://www.pmda.go.jp/files/000153901.pdf
4	Removal of Tubes and Lines	Before changing the patient’s body position or moving the patient, make sure to carefully observe whether lines will be caught, and confirm whether infusion stands and drainage bags should be moved. PMDA Medical Safety Information No. 36 “Accidental Removal of Tubes and Lines” https://www.pmda.go.jp/files/000153760.pdf

No.	Content	Preventative Measures for Recurrence and Related Notifications
5	Subcutaneous catheter fracture due to long-term and physical stress	Be cautious about fractures, etc. associated with long-term use. In addition, if a subcutaneous catheter is placed in the subclavian vein, make sure that the catheter is not pinched between the first rib and the clavicle. PFSB/SD Notification No. 0525-1 and PFSB/ELD/OMDE Notification No. 0525-1 dated May 25, 2011, "Revisions of Package Inserts Related to Subcutaneous Ports and Catheters" (Only available in the Japanese language) http://www.pmda.go.jp/files/000148739.pdf *Pharmaceuticals and Medical Devices Safety Information No. 281 Review Commentary (Only available in the Japanese language) http://www1.mhlw.go.jp/kinkyu/iyaku_j/iyaku_j/anzenseijyouhou/281-1.pdf

3. Requests to Healthcare Professionals

Preventative measures for recurrence and related notifications have been presented this time for each distinct recurrent incident.

In addition to re-confirming the management structure within the facility, please refer to the aforementioned information when providing guidance to patients and family, etc. Please also refer to PMDA Medical Safety Information for details of other incidents for which caution should be exercised.

(References)

1 MHLW: Survey on Safe Use of Pharmaceuticals and Medical Devices (Only available in the Japanese language)
http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000057965.html

2 PMDA: Survey Results on Safe Use of Pharmaceuticals, Medical Devices, and Regenerative Medicines (Only available in the Japanese language)
http://www.pmda.go.jp/safety/info-services/medical-safety-info/0004.html

3 PMDA Medical Safety Information
https://www.pmda.go.jp/english/safety/info-services/safety-information/0001.html

3
Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated September 15, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Asunaprevir and Daclatasvir hydrochloride

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

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Thrombocytopenia: Thrombocytopenia may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 11 months (from initial marketing to July 2015).
Cases of adverse reactions associated with thrombocytopenia:
8 cases* (no fatal cases)
*Cases for which a causality to combination therapy of asunaprevir and daclatasvir hydrochloride could not be ruled out
The number of patients using this drug estimated by the marketing authorization holder (MAH): Approximately 39 500 (from initial marketing to June 2015)
Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Chronic hepatitis C (scleroderma, interstitial lung disease (ILD))	Daklinza Tablets 60 mg and Sunvepra Capsules 200 mg for 70 days	**Thrombocytopenia, liver disorder** No history of prior treatment. No previous medical history. Day 1 of administration: Combination therapy with Daklinza Tablets 60 mg once daily and Sunvepra Capsules 100 mg twice daily was started. Day 56 of administration: Elevation of aspartate aminotransferase (AST) to 178 IU/L and alanine aminotransferase (ALT) to 206 IU/L. Begin follow-up by conducting blood tests 2-3 times a week. Platelet (Plt) count was $14.0\times10^4/mm^3$. Date unknown: ALT levels fluctuated between 180 IU/L and 200 IU/L. Day 70 of administration (day of discontinuation):

Elevation of AST levels to 293 IU/L and ALT levels to 297 IU/L. The patient was admitted to the hospital due to liver disorder.
Onset of thrombocytopenia. Plt decreased to $4.2\times10^4/mm^3$. Administration of Daklinza Tablets and Sunvepra Capsules was discontinued.
1 day after discontinuation:
Plt decreased to $1.1\times10^4/mm^3$ in the morning and $0.7\times10^4/mm^3$ in the evening; therefore, the patient was transfused with 10 units of platelets. AST level was 329 IU/L and ALT level was 314 IU/L.
2 days after discontinuation:
Plt was $0.8\times10^4/mm^3$; therefore, the patient was transfused with 10 units of platelets.
3 days after discontinuation:
Plt was $0.6\times10^4/mm^3$; therefore, the patient was transfused with 15 units of platelets. Plt did not increase and was $0.5\times10^4/mm^3$ 1 hour after transfusion.
4 days after discontinuation:
Plt remained low at $0.4\times10^4/mm^3$. Because the patient showed limited response to transfusion, opted to observe rather than transfuse.
13 days after discontinuation:
Plt was $4.5\times10^4/mm^3$ and resolving.
17 days after discontinuation:
Thrombocytopenia and liver disorder were resolving.

Laboratory examination

	42 days before administration	1 day before administration	Day 56 of administration	Day 70 of administration (Day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation
PLT ($\times10^4/mm^3$)	14.2	10.4	14.0	4.2	1.1	0.8	0.6
AST (IU/L)	108	8	178	293	329	288	234
ALT (IU/L)	146	70	206	297	314	294	263
T-Bil (mg/dL)	0.4	0.3	0.5	0.6	0.7	-	-
WBC ($/mm^3$)	4 300	4 100	7 400	5 400	4 400	-	-
RBC ($\times10^4/mm^3$)	349	326	348	347	328	-	-
Hb (g/dL)	10.9	10.9	10.5	10.7	10.2	-	-

	4 days after discontinuation	7 days after discontinuation	8 days after discontinuation	10 days after discontinuation	13 day after discontinuation	15 days after discontinuation	17 days after discontinuation
PLT ($\times10^4/mm^3$)	0.4	0.5	0.8	1.6	4.5	6.0	7.7
AST (IU/L)	174	-	103	83	51	51	46
ALT (IU/L)	220	-	133	108	61	53	45
T-Bil (mg/dL)	0.7	-	-	-	0.5	-	-
WBC ($/mm^3$)	4 200	-	-	-	4 100	-	-
RBC ($\times10^4/mm^3$)	352	-	-	-	352	-	-
Hb (g/dL)	10.4	-	-	-	10.6	-	-

Concomitant medications: tocopherol nicotinate

2 Amantadine hydrochloride

Brand name (name of company)	Symmetrel Tablets 50 mg, 100 mg, and Symmetrel Fine Granules 10% (Novartis Pharma K.K.), and the others
Therapeutic category	Antiparkinsonian agents
Indications	Parkinson's syndrome Improvement of hypobulia or decreased initiative associated with sequela of cerebral infarction Type A influenza virus infection

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

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

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (from April 2012 to June 2015).
Cases of adverse reactions associated with rhabdomyolysis:
1 case (no fatal case)
The number of patients using this drug estimated by the MAH:
Approximately 41 000 (from August 2014 to July 2015)
Launched in Japan: December 1975

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Parkinsonism (hypertensive angiopathy, cerebral haemorrhage, normal pressure hydrocephalus, gastritis, constipation)	50 mg for 55 days	**Rhabdomyolysis, vomiting** Unknown: The patient was admitted to the hospital due to hypertensive subcortical haemorrhage. Administration of amlodipine and polaprezinc was started. The patient was discharged from the hospital after rehabilitation. Unknown: The patient complained about nausea and vomiting. Day 1 of administration: Administration of Symmetrel Tablets 50 mg/day was started to treat Parkinsonism (after hypertensive subcortical haemorrhage). Approximately 1 month after initiating administration: The patient vomited. Day 49 of administration: The patient was admitted to the hospital again due to complains about nausea and vomiting. The patient was diagnosed as normal pressure hydrocephalus. The patient also complained about myalgia. Myogenic enzymes increased. Day 52 of administration: The patient complained about myalgia and was vomiting. Myogenic enzymes further increased. Day 53 of administration: Administration of amlodipine was discontinued.

<table>
<tr><td></td><td></td><td></td><td></td><td>Day 55 of administration (day of discontinuation):
Administration of Symmetrel Tablets was discontinued. Fluid replacement was conducted.
4 days after discontinuation:
The patient did not complain about myalgia. No vomiting was observed.
11 days after discontinuation:
The patient did not complain about myalgia. No vomiting was observed. Decrease in myogenic enzymes.
32 days after discontinuation:
The patient did not complain about myalgia. No vomiting was observed. Myogenic enzymes recovered to normal.</td></tr>
<tr><td></td><td colspan="4">Laboratory examination
<table>
<tr><th></th><th>Day 49 of administration</th><th>Day 52 of administration</th><th>11 days after discontinuation</th><th>32 days after discontinuation</th></tr>
<tr><td>AST (IU/L)</td><td>99</td><td>430</td><td>20</td><td>9</td></tr>
<tr><td>LDH (IU/L)</td><td>489</td><td>955</td><td>408</td><td>220</td></tr>
<tr><td>CK (CPK) (IU/L)</td><td>829</td><td>4 498</td><td>76</td><td>-</td></tr>
<tr><td>CK (CPK) –MB (IU/L)</td><td>37</td><td>-</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant medications: amlodipine besilate, polaprezinc, magnesium oxide, sennoside</td></tr>
</table>

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

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.

Adverse reactions (clinically significant adverse reactions)

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

Colitis and severe diarrhoea: Colitis or severe diarrhoea may occur. Patients should be carefully monitored. If symptoms such as persistent diarrhoea, abdominal pain, and haematochezia are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 1 year and 1 month (from July 2014 to July 2015).
Cases of adverse reactions associated with myasthenia gravis and myositis: 6 cases (1 fatal case)
Cases of adverse reactions associated with colitis and severe diarrhoea: 4 cases (no fatal case)
The number of patients using this drug estimated by the MAH: Approximately 855 (from July 2014 to June 2015)
Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Malignant melanoma (chronic thyroiditis, osteoarthritis, spondylolisthesis, lumbar vertebral fracture, hypertension, hyperlipidaemia, osteoporosis,	2 mg/kg 1 course every 3 weeks	**Myasthenia gravis, myopathy** Approximately 3 years before administration: Resection of malignant skin cancer and biopsy of the left inguinal sentinel lymph node was conducted for malignant melanoma (left hallux, Stage IIB). After these procedures were conducted, the patient suffered from metastasis in the lymph nodes, lungs, and skin. Thyroid testing was conducted before administration of Opdivo, and, although the patient tested positive for auto-antibodies (thyroid peroxidase (TPO) antibodies), free triiodothyronine (FT3) and thyroxine (FT4) were within

		cataract)		normal ranges and the patient had no symptoms. Day 1 of administration: Administration of Opdivo (2 mg/kg/day) was started. Approximately Day 13 of administration: Onset of malaise, shortness of breath during exertion, and myalgia. Day 20 of administration: The patient consulted the hospital due to gradual exacerbation of symptoms. The patient suffered from muscle weakness of proximal limb muscles and myalgia, and was admitted to the hospital due to increase in CK (8 729 IU/L), AST (611 IU/L), and ALT (359 IU/L). Day 21 of administration: Based on the laboratory data, the patient was diagnosed with rhabdomyolysis and hepatic function disorder. No abnormalities in renal function were observed. The patient was initiated on 500 mL/hour of fluid replacement and the amount of liquid transfused was adjusted so that urinary output per hour was 100 mL. Administration of methylprednisolone (125 mg/day) was started. Although AST and ALT was slightly resolving, CK barely changed. Onset of breathing difficulties and paradoxical breathing. Day 22 of administration: Although myalgia was resolving, breathing difficulty worsened. Harvey-Masland test and Edrophonium (Tensilon) test were conducted by the neurology department. Although no significant findings were observed, the patient was suspected to be suffering from myasthenia gravis due to muscle weakness mainly in proximal limb muscles and onset of eyelid ptosis and diplopia. Confirmed (using an echo) that respiratory failure was being caused by poor diaphragm movement. Oxygen saturation (SpO_2) was 95% with use of nasal oxygen 3L/minute, after which SpO_2 was 92% with oxygen 5L/minute. Because the patient complained of severe breathing difficulties, ILD was also suspected. Day 24 of administration: A pulmonologist was consulted. Chest computed tomography (CT) tests showed no abnormalities in the lung field; therefore, possibility of ILD was negated. Diaphragm movements seemed bad. The patient continued to suffer from respiratory failure. Adenocorticotropic hormone levels were within the normal range (actual values were unconfirmed). The patient tested positive for anti-TPO antibodies and physicians were concerned about rhabdomyolysis associated with hypothyroidism; however, given that FT3 and FT4 did not fluctuate greatly even though thyroid stimulating hormone levels were low, the possibility of rhabdomyolysis associated with hypothyroidism was negated. Furthermore, the patient was untreated with quinolone antibiotic which is prone to cause rhabdomyolysis, and the patient had no prior history of being treated with interferon-alpha, which may cause rhabdomyolysis as an adverse reaction. Pleural effusion was only seen in the left lung. Cardiac failure was not a complication. Possibility of cancerous pleurisy was considered to be low. Myalgia in the shoulders

				were recovering and levels of myogenic enzymes started to stabilize. Day 27 of administration: The patient died due to exacerbation of respiratory failure. Respiratory conditions prior to death were SpO_2 92% with oxygen 5L (intubation and non-invasive positive pressure ventilation could not be conducted due to patient and family request). Dyslalia was not observed

Laboratory examination

	Prior to administration	Day 1 of administration	Day 20 of administration	Day 21 of administration	Day 22 of administration	Day 23 of administration	Day 24 of administration	Day 25 of administration
CK (IU/L)	-	105	8 729	7 943	6 976	4 389	2 581	2 161
AST (IU/L)	-	26	611	615	605	441	249	178
ALT (IU/L)	-	15	359	361	403	416	351	313
FT3 (pg/mL)	2.81	3.05	1.50	1.5	-	-	0.97	-
FT4 (ng/dL)	1.03	1.02	1.16	1.16	-	-	0.73	-
TSH (mU/L)	2.1	3.34	0.087	0.089	-	-	0.148	-
K (mmol/L)	3.9	4	4.4	3.9	-	-	3.7	-
Arterial pH	-	-	7.434	7.453	-	-	7.331	7.362
pCO_2 (mmHg)	-	-	39.4	39.7	-	-	60.1	57.9
pO_2 (mmHg)	-	-	66.5	49.2	-	-	67.8	69.6
HCO_3 (mmol/L)	-	-	25.9	27.3	-	-	30.9	32
BE (mmol/L)	-	-	2.1	3.6	-	-	3.7	5.3

Before administration: Anti-TPO antibody; positive
Day 20 of administration: Anti-Jo-1 antibody; negative
Day 20 of administration: No abnormalities observed in chest X-ray and CT
Day 24 of administration: Anti-acetylcholine receptor antibody: positive (12.4 nmol/L)
Day 24 of administration: Anti-aminoacyl tRNA synthetase antibody: negative
Day 24 of administration: Anti-muscle specific tyrosine kinase receptor antibody: negative
Day 24 of administration: Electromyogram (Harvey-Masland test); negative
Day 24 of administration: Low frequency repetitive stimulation test of the right accessory nerve/trapezius; waning 9.7%
Day 24 of administration: Nerve conduction test; decrease in compound muscle action potential
Day 24 of administration: Ultrasound exam; Bad diaphragm movement

Concomitant medications: alendronate sodium hydrate, loxoprofen sodium hydrate, teprenone, amlodipine besilate, montelukast sodium, lansoprazole, atorvastatin calcium hydrate, olmesartan medoxomil, intravenous injection of thiamine disulfide phosphate/B6/B12 fixed-dose combination, methylprednisolone sodium succinate, furosemide, omeprazole sodium, human serum albumin

4 Sodium glucose co-transporter 2 (SGLT2) inhibitors

1. Ipragliflozin L-proline
2. Tofogliflozin hydrate
3. Luseogliflozin hydrate

Brand name (name of company)	1. Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc.) 2. Apleway Tablets 20 mg (Sanofi K.K.), Deberza Tablets 20 mg (Kowa Company, Ltd.) 3. Lusefi Tablets 2.5 mg, 5 mg (Taisho Pharmaceutical Co., Ltd.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Important precautions

Urinary tract infection may occur, which may lead to severe infections such as pyelonephritis and sepsis. Genital infections such as vaginal candidiasis may also occur. Patients should be carefully monitored for urinary tract infection and genital infection. If infection occurs, appropriate measures should be adopted, and measures such as temporary discontinuation of this drug should be taken into consideration based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.

Due to the mechanism of action which accelerates secretion of urinary glucose, metabolism of fatty acids may increase and cause ketosis, which can then lead to ketoacidosis even if blood glucose is controlled. Significant increase in blood glucose level may not occur in such cases; therefore, caution should be exercised for the following points.

1. If symptoms such as nausea/vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnoea, and/or disturbed consciousness are observed, laboratory tests including those that measure blood and urinary ketone bodies should be conducted. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.
2. The following patients are especially susceptible to developing ketoacidosis and should be carefully monitored: patients who experienced decreased insulin secretion function, dosage reduction or discontinuation of administration of insulin products, excessively restrict sugar intake, poor feeding habits, infection, or dehydration.
3. Inform patients about the symptoms of ketoacidosis (such as nausea/vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnoea, and/or disturbed consciousness), and instruct them to seek medical attention immediately, if they experience such symptoms.

Adverse reactions (clinically significant adverse reactions)

Pyelonephritis and sepsis: Pyelonephritis may occur, which may lead to sepsis (including septic shock). Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Ketoacidosis: Ketoacidosis (including diabetic ketoacidosis) 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) recently (from initial marketing to July 2015).

Cases of adverse reactions associated with ketoacidosis:

1. 9 cases (no fatal case)
2. 2 cases (no fatal case)
3. 1 case (no fatal case)

Cases of adverse reactions associated with sepsis:

1. 6 cases (no fatal case)
2. 3 cases (no fatal case)
3. No reported cases

The number of patients using this drug estimated by the MAH:

1. Approximately 130 000 (from initial marketing to May 2015)
2. Approximately 25 000 (from initial marketing to April 2015)
3. Approximately 21 000 (from initial marketing to April 2015)

Launched in Japan:

1. April 2014
2. May 2014
3. May 2014

4. Empagliflozin
5. Canagliflozin hydrate
6. Dapagliflozin propylene glycolate hydrate

Brand name (name of company)	4. Jardiance Tablets 10 mg, 25 mg (Nippon Boehringer Ingelheim Co., Ltd.) 5. Canaglu Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation) 6. Forxiga Tablets 5 mg, 10 mg (AstraZeneca K.K.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Careful administration

Patients with urinary tract infection and/or genital infection

Important precautions

Urinary tract infection may occur, which may lead to severe infections such as pyelonephritis and sepsis. Genital infections such as vaginal candidiasis may also occur. Patients should be carefully monitored for urinary tract infection and genital infection. If infection occurs, appropriate measures should be adopted, and measures such as temporary discontinuation of this drug should be taken into consideration based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.

Due to the mechanism of action which accelerates secretion of urinary glucose, metabolism of fatty acids may increase and cause ketosis, which can then lead to ketoacidosis even if blood glucose is controlled. Significant increase in blood glucose level may not occur in such cases; therefore, caution should be exercised for the following points.

1. If symptoms such as nausea/vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnoea, and/or disturbed consciousness are observed, laboratory tests including those that measure blood and urinary ketone bodies should be conducted. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.
2. The following patients are especially susceptible to developing ketoacidosis and should be carefully monitored: patients who

experienced decreased insulin secretion function, dosage reduction or discontinuation of administration of insulin products, excessively restrict sugar intake, poor feeding habits, infection, or dehydration.

3. Inform patients about the symptoms of ketoacidosis (such as nausea/vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnoea, and/or disturbed consciousness), and instruct them to seek medical attention immediately, if they experience such symptoms.

Adverse reactions (clinically significant adverse reactions)

Pyelonephritis and sepsis: Pyelonephritis may occur, which may lead to sepsis (including septic shock). Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Ketoacidosis: Ketoacidosis (including diabetic ketoacidosis) 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) recently (from initial marketing to July 2015).

Cases of adverse reactions associated with ketoacidosis:

4. No reported case
5. 2 cases, of which 1 case was for a condition not included in the approved indications (no fatal case)
6. 5 cases, of which 1 case was for a condition not included in the approved indications (no fatal case)

Cases of adverse reactions associated with sepsis:

4. No reported case
5. No reported case
6. 3 cases (no fatal case)

The number of patients using this drug estimated by the MAH:

4. Approximately 22 000 (from initial marketing to May 2015)
5. Approximately 13 000 (from initial marketing to April 2015)
6. Approximately 60 000 (from initial marketing to May 2015)

Launched in Japan:

4. February 2015
5. September 2014
6. May 2014

Case summary for Ipragliflozin L-proline

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	Type 2 diabetes mellitus (Prader-Willi syndrome)	50 mg 13 days	**Ketoacidosis** Date unknown: The patient developed type 2 diabetes mellitus due to Prader-Willi syndrome in her 10s and began oral medications and calorie restriction at Hospital A (the patient tested positive for urinary glucose). Date unknown: Switched from calorie restriction diet to sugar restriction diet (low-carb diet) at Hospital B in her 20s (restricted to 60 g of carbohydrates per day). 3 years before administration: Administration of 14 units of insulin glargine and metformin hydrochloride was started. 1 year and 8 months before administration: Sitagliptin was added-on to previous treatment. 1 year and 3 months before administration: Administration of sitagliptin was discontinued and

				administration of acarbose was started. 1 year and 2 months before administration: Administration of acarbose was discontinued and administration of vildagliptin was started. 7 months before administration: Administration of linagliptin, glimepiride 1 mg, and metformin hydrochloride 2 250 mg was started. A few days before administration: The patient had cold symptoms mainly constituting of a runny nose, abdominal pain, malaise, and slight fever (37.1°C). Day 1 of administration: Administration of Suglat Tablet 50 mg/day was started. Administration of all other drugs was discontinued. A few days after beginning administration: Onset of pollakiuria and weight decrease (3 kg/7-10 days). Day 12 of administration: The patient complained of abdominal pain, and the amount of food and fluid ingested decreased. No symptoms such as diarrhoea or vomiting were observed. The patient proactively drank fluids without any sugar. The patient's diet mainly constituted of bran bread, vegetables, and meat. Day 13 of administration (day of discontinuation): Onset of tachypnoea which lead to the patient being emergently transported to the hospital. At the time of consultation, pH was 7.055, base excess (BE) was -25.3 mmol/L, urinary ketone was 3+, an increase was seen in blood ketone, and bicarbonate ion (HCO_3) was 3.0; therefore, the patient was confirmed to have metabolic acidosis. Anion gap (AG) also increased to 28.0. Corrected HCO_3 was 15.6<26, indicating that there was no metabolic alkalosis complications. Potassium (K) levels were low. The patient did not have diarrhoea. The patient's blood glucose level was 185 mg/dL, which was not that high. C peptide levels were also fairly low. The patient was admitted to the hospital with a diagnosis of ketoacidosis. Administration of Suglat Tablet was discontinued. 1 day after discontinuation: Intravenous infusion of 6 units of human insulin and 500 mL of electrolyte transfusion fluid (maintenance fluid with 7.5% sugar) was started. 3 days after discontinuation: Ketoacidosis was resolving with massive transfusion, insulin administration, and glucose fluid administration. 6 days after discontinuation: Central venous line and urinary balloon were removed. Energy restriction diet (1 520 kcal, 65 g of protein, 45 g of lipids, and 210 g of carbohydrates) was requested. The patient was able to consume 90% of her meal and C peptide levels began to increase gradually. 22 days after discontinuation: The patient achieved good blood glucose control with administration of insulin glargine 24 units, lixisenatide 20 mg, and metformin hydrochloride 2 250 mg, and was discharged from the hospital.

	Laboratory examination See table below
	Concomitant medications: timepidium bromide hydrate, pyrazolone derivative antipyretics/analgesics/anti-inflammatory agent fixed-dose combination, diclofenac sodium

	Day 13 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	6 days after discontinuation
AG	28.0	18.7	-	-	-
BE (mmol/L)	-25.3	-9.4	-	-	-
Glu (mg/dL)	185	146	-	-	183
Acetobutyrate (μmol/L)	-	1 915	1 288	617	78
Total ketone (μmol/L)	-	7 473	5 305	2 742	435
Urinary C peptide (μg/day)	-	-	2.0>	3.1	26.8
Arterial pH	7.055	7.374	-	-	-
HCO_3 (mEq/L)	3.0	13.8	-	-	32.4
K (mEq/L)	3.4	2.2	-	-	4.0

Case summary for Dapagliflozin propylene glycolate hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 40s	Type 2 diabetes mellitus (muscular dystrophy, uterine leiomyoma, cataract, chronic gastritis, iron deficiency anaemia, constipation, dyspepsia, gastroenteritis)	5 mg Unknown	**Metabolic acidosis (ketoacidosis)** Approximately 20 years ago: The patient was diagnosed as type 2 diabetes mellitus. Begin administration (date unknown): Administration of Forxiga Tablets was started due to poor blood glucose control. 1 month before onset: Hemoglobin A1c (HbA1c) was 8.1%. 17 days before onset: Onset of diarrhoea was observed in the patient and continued while the patient was consulting a different hospital. Day of onset: Pyrexia 38°C and above, cough, sputum, and headache were observed, and the patient suffered from decreased appetite. (Onset of acute upper respiratory inflammation and metabolic acidosis). 1 day after onset: Although the patient was able to consume small amounts of food, she became unable to ingest any solids hereon after. The patient also only consumed a small amount of liquid. 3 days after onset: The patient consulted a physician nearby and was prescribed tulobuterol tape (2 mg/day), azithromycin (500 mg/day), and dextromethorphan (60 mg/day). The patient was not instructed to suspend usage of preceding treatment. 4 days after onset: The patient was emergently transported to the hospital at midnight due to poor general conditions. Blood glucose levels were 184 mg/dL, pH was 7.107, acetoacetate was 1 943 μmol/L, 3-hydroxy-butyrate was 13 189 μmol/L, and total ketone bodies was 15 132 μmol/L.

				5 days after onset (day of discontinuation): Arterial gas analysis conducted before dawn onwards indicated a widening of AG and that the patient was suffering from metabolic acidosis. The patient was diagnosed as diabetic ketoacidosis based on the blood lactate levels, which were 0.7 (normal). pH was 7.282. Sufficient amount of fluid replacement (extracellular fluid), insulin administration, and correction by $NaHCO_3$ and potassium formulations was carried out. Lactobacillus bifidus preparations was administered for diarrhoea. All oral drugs were discontinued including Forxiga Tablets. 3 days after discontinuation: Urinary ketone body remained at (4+). Acidosis was resolving. 5 days after discontinuation: Metabolic acidosis and diarrhea was resolved.

Laboratory examination

	1 month before onset	Day of onset	4 days after onset	Day of discontinuation		1 day after discontinua-tion	3 days after discontinua-tion	5 days after discontinua-tion	13 days after discontinua-tion
				5:00	13:00				
Blood glucose (mg/dL)	130 (fasting)	-	184	-	-	128	-	97	-
HbA1c (%)	8.1	-	-	-	-	-	-	-	-
Max body temp. (°C)	-	≥38	36.9	37.0	37.4	37.4	37.0	36.7	-
BUN (mg/dL)	-	-	10	-	-	6	3	9	8
SCr (mg/dL)	-	-	0.32	-	-	0.29	0.20	0.25	0.27
Na (mEq/L)	-	-	142	-	-	150	140	141	142
K (mEq/L)	-	-	3.2	-	-	4.4	4.6	4.2	4.3
Cl (mEq/L)	-	-	108	-	-	114	101	103	105
CRP (mEq/L)	-	-	0.29	-	-	0.20	1.03	0.71	0.12
Urinary ketone body	-	-	(4+)	-	-	-	(4+)	(-)	(-)
pH	-	-	7.107	7.282	7.148	7.345	7.48	-	-
BE (mEq/L)	-	-	-23.0	-14.9	-20.5	-7.9	8.0	-	-
Lactic Acid (mmol/L)	-	-	-	0.7	-	-	-	-	-
Acetoacetate (μmol/L)	-	-	1 943	-	-	-	-	-	-
3-hydroxy-butyrate (μmol/L)	-	-	13 189	-	-	-	-	-	-
Total ketone body (μmol/L)	-	-	15 132	-	-	-	-	-	-
Blood CPR (μg/ml)	-	-	-	-	-	-	0.87	-	-
Urinary CPR (μg/day)	-	-	-	-	-	-	71.1	-	-
Anti-GAD antibody (/ml)	-	-	-	-	-	-	<0.30	-	-
Urinary acetone	-	-	-	-	-	-	-	-	(-)
WBC response	-	-	-	-	-	-	-	-	(-)

Concomitant medications: teneligliptin hydrobromide hydrate, pioglitazone hydrochloride, acotiamide hydrochloride hydrate, lubiprostone, mosapride citrate hydrate, magnesium oxide, Lactobacillus bifidus preparations, sodium ferrous citrate, rebamipide

Case summary for Ipragliflozin L-proline

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/
Age</th><th>Reason for use
(complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>3</td><td>Woman
50s</td><td>Type 2 diabetes mellitus</td><td>50 mg
29 days</td><td>Sepsis, Escherichia pyelonephritis
The patient suffered from left side paralysis due to a past traffic accident and was unable to carry out exercise therapy for diabetes mellitus.
Day 1 of administration:
Administration of Suglat Tablets 50 mg/day was started by Hospital A to treat type 2 diabetes mellitus.
Day 27 of administration:
Blood glucose levels were 126 mg/dL (normal range: 70-109 mg/dL) and glycohemoglobin was 9.7% (normal range: 4.6-6.2%)
Date unknown:
Onset of pyelonephritis.
Day 29 of administration (day of discontinuation):
The patient was unable to stand on her own at this point. Onset of sepsis. Administration of Suglat is discontinued.
1 day after discontinuation:
The patient consulted the emergency outpatient ward of Hospital B and claimed to be suffering from sickness. Based on the laboratory test results, the patient was diagnosed with pyelonephritis and sepsis. The patient was concomitantly suffering from disseminated intravascular coagulation (DIC). The patient was admitted to the hospital, and medical treatment was started with antibiotic (doripenem hydrate), globulin products, thrombomodulin alfa, and noradrenaline. Polymyxin B-immobilized fiber (PMX) (endotoxin adsorption therapy), and continuous hemodiafiltration (CHDF) was administered the first day.
2 days after discontinuation:
PMX and CHDF conducted a second time.
6 days after discontinuation:
Identified Escherichia coli as the causative pathogen. Switched antibiotic to cefazolin.
14 days after discontinuation:
Complete treatment with antibiotic.
21 days after discontinuation:
The patient was discharged from the hospital. Outcomes of sepsis and pyelonephritis recovered.
26 days after discontinuation:
Blood glucose levels were 194 mg/dL (normal range: 70-109 mg/dL), and glycohemoglobin was 8.1% (normal range: 4.6-6.2%)</td></tr>
<tr><td></td><td colspan="4">Laboratory examination
<table>
<tr><th></th><th>2 days before administration</th><th>Day 27 of administration</th><th>26 days after administration</th></tr>
<tr><td>Glu (mg/dL)</td><td>212</td><td>126</td><td>194</td></tr>
<tr><td>HbA1c (NGSP) (%)</td><td>10.0</td><td>9.7</td><td>8.1</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant medications: loxoprofen sodium hydrate, fexofenadine hydrochloride, insulin, sitagliptin phosphate hydrate, sennoside, fesoterodine fumarate, insulin glargine</td></tr>
</table>

Case summary for Tofogliflozin hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female 80s	Type 2 diabetes mellitus (cerebral infarction, dementia)	20 mg (unknown)	**Sepsis, hyperglycaemic hyperosmolar nonketotic syndrome, urinary tract infection, multi-organ failure, DIC, septic shock** Approximately 2 months before onset: Based on records in the medication record book, the patient was being treated for diabetes with sitagliptin phosphate hydrate and glimepiride until 2 months before onset of adverse reactions. Glimepiride was switched to Lusefi Tablets approximately 2 months before onset. The patient had dementia and decreased activities of daily living and was unable to eat properly; therefore, family members were having to force feed the patient. 4 days before onset: The patient's subcutaneous haemorrhage symptoms strengthened; therefore, she was admitted to the hospital of her previous physician. 1 day before onset: Conditions were diagnosed to be caused by excess efficacy of warfarin potassium and the patient was being treated accordingly; however, the patient developed somnolence tendencies and blood glucose levels were 470 mg/dL. Day of onset: Although the patient was initiated on insulin treatment, it was not effective, and the patient was emergently transported to a different hospital because her conditions scored 300 points on the Japan Coma Scale (JCS). (No abnormalities were observed in head MRI or CT scans conducted by the previous physician.) At time of consultation, JCS scores were 300 points, blood pressure was 51/28, and pulse was 140/min, and the patient was going into shock. Treatment with dopamine and transfusion was initiated, and the patient was taken for further examination. Blood glucose levels were extremely high at 658 mg/dL, and, although urinary ketones tested negative, the patient was suffering from severe dehydration, anaemia, hepatic function abnormal, renal function abnormal and multiple organ failure based on blood test results. Blood urea nitrogen (BUN) levels were 99 mg/dL; creatinine (CRE) levels were 2.61 mg/dL, uric acid (UA) levels were 11.3 mg/dL; sodium (Na) levels were 147 mEq/L; K levels were 2.7 mEq/L; chloride (Cl) levels were 109 mEq/L; white blood cell (WBC) count was 22 300/μL; Hb levels were 5.2 g/dL; Plt count was 63 000/μL; prothrombin time (international normalized ratio) was 1.90; blood fibrin/fibrinogen degradation products quantitative levels were 16 μg/mL; casual blood glucose was 658 mg/dL; general qualitative urine analysis was (glucose qualitative 4+, WBC 3+); urinary sedimentation was (WBC 100≤/H, bacteria 3+, cell clump +, fungus +); C-reactive protein (CRP) was

8.2 mg/dL, procalcitonin (PCT) levels were ≥10 ng/mL. These test values indicated an infection, and, based on the fact that there were no abnormalities observed in the CT scans, it was anticipated that urinary tract infection was the focus. After admitting the patient to the hospital, massive fluid replacement and continuous administration of insulin was initiated to treat hyperosmolar hyperglycaemic syndrome. The patient was also administered antibiotics for the urinary tract infection. With recovering blood glucose levels and dehydration, diuretic effects were also observed.

29 days after onset:

Blood glucose levels, dehydration, and renal function were gradually resolving. Although conscious level recovered slightly, the patient's condition was still 200 points on JCS. BUN was 17 mg/dL; CRE was 0.73 mg/dL; UA was 3.1 mg/dL; WBC was 9 700/μL; Hb was 8.2 g/dL; and Plt was 190 000/μL.

36 days after onset:

Acute treatment was completed and the infection was under control; therefore, the patient was moved to a different hospital.

Laboratory examination

	Day of onset	29 days after onset
Plt ($\times 10^4/mm^3$)	6.3	19
WBC ($/mm^3$)	22 300	9 700
BUN (mg/dL)	99	17
Serum CRE (mg/dL)	2.61	0.73
Blood glucose (mg/dL)	658	-
UA (mg/dL)	11.3	3.1
RBC ($\times 10^4/mm^3$)	172	271
Hematocrit (%)	16	25
CRP quantitative (mg/dL)	8.22	2.3
Urinary coloration	Cloudy	Clear
Urinary occult blood	(3+)	(-)
Urinary WBC	(3+)	(-)
Urinary bacteria	(3+)	(-)
PCT (ng/mL)	≥10	-

Concomitant medications: sitagliptin phosphate hydrate, cilostazol, warfarin potassium, lansoprazole, furosemide, raloxifene hydrochloride

4

Revision of Precautions (No. 268)

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 September 15, 2015.

1

Miscellaneous metabolism agents

Fingolimod hydrochloride

Brand name	Gilenya Capsules 0.5 mg (Novartis Pharma K.K.) and Imusera Capsules 0.5 mg (Mitsubishi Tanabe Pharma Corporation)
Adverse reactions (clinically significant adverse reactions)	**Progressive multifocal leukoencephalopathy (PML)**: PML may occur. Patients should be carefully monitored during and after treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, symptoms of paralysis (hemiplegia or quadriplegia), or speech and language disorder are observed, imaging diagnostics with MRI and cerebrospinal fluid tests should be performed. In addition, administration of this drug should be discontinued, and appropriate measures should be adopted.

2

Antibiotics acting mainly on gram-positive bacteria and mycoplasma

Azithromycin hydrate

Brand name	Zithromac Tablets 250 mg, Zithromac Capsules for pediatric use 100 mg, Zithromac Fine Granules for pediatric use 10%, Zithromac SR Dry Syrup 2 g, Zithromac Tablets 600 mg, Zithromac Intravenous Infusions 500 mg (Pfizer Japan Inc.) and the others
Adverse reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome (DIHS)**: Rash and/or pyrexia may occur as initial symptoms, followed by serious late-onset hypersensitivity symptoms with hepatic function disorder, lymphadenopathy, increased white blood cells (WBC), increased eosinophils, atypical lymphocytes, etc. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be adopted. The reactivation of viruses including Human Herpes Virus 6 (HHV-6) has been frequently found associated with DIHS. Symptoms such as rash, pyrexia, and/or hepatic function disorder may relapse or be prolonged even after discontinuation of administration, and therefore, caution should be exercised.

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 adverse drug reactions (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, 2015)
◎: Products for which EPPV was initiated after September 1, 2015

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

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

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
peginterferon alfa-2b (genetical recombination) Peginteron Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, 150 μg/0.5 mL	MSD K.K.	May 26, 2015
ramosetron hydrochloride Irribow Tablets 2.5 μg and 5 μg[*15], Irribow OD Tablets 2.5 μg and 5 μg[*15]	Astellas Pharma Inc.	May 26, 2015
duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg[*16]	Shionogi & Co., Ltd.	May 26, 2015
nalfurafine hydrochloride Nopicor Capsules 2.5 μg[*17]	Toray Medical Co., Ltd.	May 26, 2015
aripiprazole hydrate Abilify prolonged release aqueous suspension for IM injection 300 mg and 400 mg, Abilify prolonged release aqueous suspension for IM injection 300 mg Syringe and 400 mg Syringe	Otsuka Pharmaceutical Co., Ltd.	May 25, 2015
colistin sodium methanesulfonate Aldreb for Injection 150 mg	GlaxoSmithKline K.K.	May 25, 2015
(1) sofosbuvir, (2) ribavirin (1) Sovaldi Tablets 400 mg, (2) Copegus Tablets 200 mg[*18]	(1) Gilead Sciences, Inc. (2) Chugai Pharmaceutical Co., Ltd.	May 25, 2015
pomalidomide Pomalyst Capsules 1 mg, 2 mg, 3 mg, 4 mg	Celgene K.K.	May 21, 2015
nalfurafine hydrochloride Remitch Capsules 2.5 μg	Toray Industries, Inc.	May 20, 2015
lenvatinib mesilate Lenvima Capsules 4 mg, 10 mg	Eisai Co., Ltd.	May 20, 2015
aclidinium bromide Eklira 400 μg Genuair 30, 400 μg Genuair 60	Kyorin Pharmaceutical Co., Ltd.	May 20, 2015
4-strain meningococcal vaccine (diphtheria toxoid conjugate) Menactra intramuscular injection	Sanofi K.K.	May 18, 2015
metronidazole Rozex Gel 0.75%	Galderma S.A.	May 11, 2015
elosulfase alfa (genetical recombination) Vimizim I.V. Infusion 5 mg	BioMarin Pharmaceutical Japan Inc.	April 23, 2015
N/A Allergen Extract Mites Subcutaneous Injections for Treatment “Torii” 10 000 JAU/mL, 100 000 JAU/mL	Torii Pharmaceutical Co., Ltd.	April 21, 2015
nitisinone Orfadin Capsules 2 mg, 5 mg, 10 mg	Astellas Pharma Inc.	April 14, 2015
dolutegravir sodium/lamivudine/abacavir sulfate Triumeq Combination Tablets	ViiV Healthcare K.K.	April 10, 2015
benzoyl peroxide Bepio Gel 2.5%	Maruho Co., Ltd.	April 1, 2015

*1 Pediatric indication and dosage
*2 Typical absence seizures
*3 Treat deep-vein thrombosis (DVT) and pulmonary embolism, and prevent DVT and pulmonary embolism from relapse
*4 Localized, residual recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy
*5 Improvement of pulmonary hypertension in the perioperative period of cardiac surgery
*6 Suppress development of digital ulcers in systemic sclerosis (scleroderma)
*7 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir
*8 Mantle cell lymphoma
*9 Pediatric dose for pain relief during skin laser therapy and indications for pain relief during pricking injection of an intravenous indwelling needle
*10 Suppress progression of functional disorders associated to amyotrophic lateral sclerosis (ALS)
*11 Strabismus
*12 Febrile neutropenia (new pediatric dose)
*13 Familial hypercholesterolemia (new pediatric dose)
*14 Postoperative adjuvant therapy for malignant melanoma
*15 Irritable bowel syndrome with diarrhoea in females
*16 Pain associated with fibromyalgia
*17 Improvement of pruritus in patients with chronic liver disease
*18 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir
*19 Improvement of pruritus in patients with chronic liver disease