Pharmaceuticals and Medical Devices Safety Information

No. 363 June 2019

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of 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 in Japanese).

Available information is listed here

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

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

Register here

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Pharmaceuticals and Medical Devices Safety Information

No. 363 June 2019

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

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

If providers of medical care and pharmaceutical products 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 providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
ACTH	Adrenocorticotropic hormone
AMED	Japan Agency for Medical Research and Development
BTC	Behind the counter
BUN	Blood urea nitrogen
CRP	C-reactive protein
CT	Computed tomography
DHEA-S	Dehydroepiandrosterone sulfate
DLST	Drug lymphocyte stimulation test
DVD	Digital versatile disk
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GH	Growth hormone
HbA1c	Hemoglobin A1c
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
Lym	Lymphocyte
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
WBC	White blood cell

1

Direct Patient Reporting System for Adverse Drug Reactions

1. Introduction

PMDA launched a patient reporting system for adverse drug reactions on its website on March 26, 2012 as a pilot program. Since then, PMDA has received “patient adverse drug reaction reporting,” which is direct reporting on adverse drug reactions from patients and their families. A system to receive reports on adverse drug reactions directly from patients has been introduced overseas including the US, the UK and the Netherlands. A full-scale operation of the patient adverse reaction reporting system was started on March 26, 2019 in Japan based on the pilot program results.

2. Direct patient reporting system for adverse drug reactions

The Direct Patient Reporting System for Adverse Drug Reactions is a program to collect information on cases of suspected adverse reactions to drugs used directly from patients/consumers who experienced such adverse reactions or their families. Collected information is to be used for the purpose of promoting safety measures for drugs, such as identifying the trends in occurrences of adverse drug reactions.

In addition to the reports via the direct reporting system that underwent a trial by PMDA during the pilot period, PMDA also receives reports by postal mail. Information to be reported is about the reporter, patient, drugs that may have caused the suspected adverse reaction, other medications used concomitantly, symptoms, and medical institutions that can be contacted for details.

PMDA may conduct a follow-up survey on the medical institution regarding the received information in order to obtain further details for analysis and assessment of adverse reaction information. Medical institutions or other relevant parties are requested to understand and cooperate with follow-up surveys.

Reported information except personal information is submitted by PMDA to MHLW at regular intervals and shared at the Pharmaceutical Affairs and Food Sanitation Council of MHLW. It is also released on the PMDA website after personal information has been processed so that it is unidentifiable. As part of the safety measures, the reported information except personal information of the reporter, the patient, etc. may also be provided to the marketing authorization holder (MAH) of the drug.

3. How to report

(1) Reporting on the website

Patients can search for the page using the phrase “patient adverse drug reaction reporting” on a major Internet search engine, or click the lower-right banner on the PMDA website (see the chart below for its location on the website) to access the “Direct patient reporting of adverse drug reactions” page (https://www.pmda.go.jp/safety/reports/patients/0004.html, only in Japanese). Patients can start reporting by clicking the “Start reporting” button after accessing “Reporting on the website” under the How to Report section and going to “Direct patient reporting of adverse drug reactions on the website.”

(source information provided only in Japanese)

(2) Report by postal mail

Patients can make a request for the reporting form (References 2) Appendix) by telephone at the reception for the request of PMDA's patients adverse reaction reporting form (03-3506-9546) or by downloading the reporting by clicking "Reporting by postal mail" under the How to Report section on the "Direct patient reporting of adverse drug reactions" page (https://www.pmda.go.jp/safety/reports/patients/0004.html, only in Japanese). After agreeing with the terms of service and filling out the form, patients should send it to the following address.

Address: Shin-Kasumigaseki Bldg., 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013
To Division for Direct patient reporting of adverse drug reactions, PMDA Safety Information/Planning and Management Department

4. Cases of patient adverse drug reaction reporting in the pilot period

A total of 717 reports were received from the launch of the direct reporting system as a pilot program to March 31, 2018. Of those reports, 676 reports included at least one prescription drug while 43 reports included at least one over-the-counter/behind-the-counter drug (OTC/BTC) drug. The therapeutic categories that were frequently reported were vaccines and psychotropics for

prescription drugs, and analgesics, anti-itchings, astringents, anti-inflammatory agents, and common cold drugs for OTC/BTC drugs.

The reports in the pilot period neither showed any new safety concerns on drugs nor included cases that were considered to require safety measures such as revision of package inserts.

5. Closing comments

Reporting on adverse drug reactions from many patients contributes to information collection from a different perspective from that of healthcare professionals and MAH and is used for safety measures such as identifying the trends in occurrence of adverse drug reaction. Since it is difficult to identify all adverse reactions of a drug before the launch, collection of adverse reaction information from patients will help safety measures to be conducted.

Of note, a different procedure is required to file for the payment of benefits based on the relief system for adverse drug reactions. Please go to a special site for the relief system (https://www.pmda.go.jp/kenkouhigai_camp/index.html, only in Japanese) for the summary of the relief system, contact information, procedures, etc.

In addition, healthcare professionals are required to report suspected adverse drug reactions they encounter in practice via the Drug and Medical Devices Safety Reporting System (https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html, only in Japanese).

References

1) Launching Direct Patient Reporting System for Adverse Drug Reactions, Document 4-1 for the third Committee on Drug Safety for fiscal 2018 dated March 22, 2019
https://www.mhlw.go.jp/content/11121000/000491117.pdf (only in Japanese)

2) PSEHB/SD Notification No. 0326-1 Direct Patient Reporting of Adverse Drug Reactions dated March 26, 2019
https://www.mhlw.go.jp/content/000493118.pdf (only in Japanese)

2
Research Project on Educational Programs for Healthcare Professionals who Engage in Interviews with Patients about Sensitive Matters

1. Medication used to treat multiple myeloma and its management

Since thalidomide as well as lenalidomide and pomalidomide with a similar structure (thalidomides) have potent teratogenicity, the marketing has been approved for indications of multiple myeloma, etc. under the approval condition that strict management procedures to prevent fetus exposure to the drugs (Thalidomide Education and Risk Management System (TERMS) and Proper management procedures for Revlimid and Pomalyst (RevMate)) should be properly followed.

Approximately 50 years have passed since the thalidomide scandal, its background event. We are concerned that this tragic history will fade into obscurity. While a generational shift continues among physicians and pharmacists, it is considered necessary to have a program to teach why both the drug and its derivatives have been managed under the TERMS and RevMate system and why management must be continued in the future, considering the history of the thalidomide scandal and the victims again. The education only makes it possible for us to understand the importance of strict proper management procedures for (teratogenic or possibly teratogenic) thalidomide.

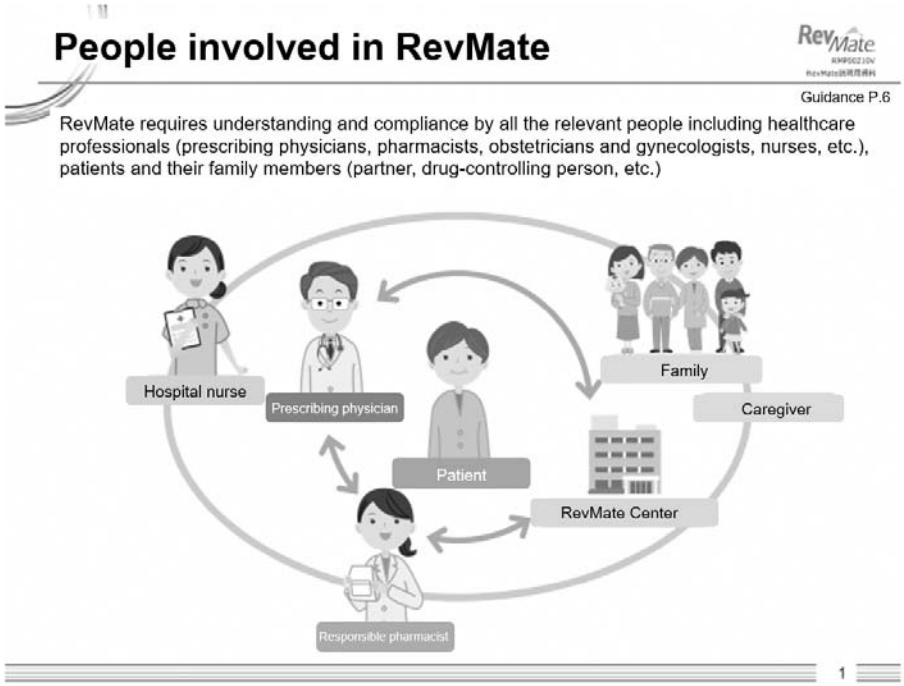
2. Communication regarding sensitive matters

The report complied in the Review Meeting on Safety Management of Thalidomide and Lenalidomide says that it is necessary to maintain the quality and the quantity of communication between patients and healthcare professionals if clinical setting is responsible for checking compliance and explanation to patients, and that it is also important not only to monitor the implementation status of safety management procedures by companies but also to enrich and enhance education for healthcare professionals for that purpose. It requires education for patients/healthcare professionals on sensitive matters including sexual intercourse and contraception as well as compliance with strict proper management procedures of thalidomide. It is essential to train the communication skills of healthcare professionals in order to appropriately obtain informed consent and to improve the quality of communication between healthcare professionals and patients by establishing the educational program for that purpose.

If patients fail to understand a message delivered by healthcare professionals, it is the senders or the healthcare professionals who are to blame for it, not the recipients (of the message) or the patients. Success in communication can be claimed only when it makes differences in the behavior of the other party of communication. Successful communication will enhance the trust of society in drugs and then the realization of safer and more satisfactory medicine can be expected. In the actual clinical practice, thorough communication taking into account scientific uncertainty is indispensable for allowing patients to make a sound “medical decision.”

The one-way communication in which healthcare professionals take initiatives and unilaterally instruct patients does not help patients remove their anxiety or doubts. Two-way communication is essential to establish a good relation between healthcare professionals and patients and will be more beneficial. Such communication also contributes to proper information provision by healthcare professionals because it allows accurate understanding of patient’s information and conditions, confirms the level of their understanding on treatment, and identifies the episodes (narratives) including each patient’s psychological aspects and social backgrounds as well as thoughts and desires (interpretation model) that the patients have in mind regarding their disease and treatment.

Medical communication aims at the best treatment given to patients, safety-information delivery (risk communication), opinion exchange among stakeholders, promotion of mutual understanding, and shared responsibility, all of which will be possible only when reliability has been established.



Provided by Celgene Corporation

3. DVD and brochures for healthcare professionals

Entrusted by the Safety Division, MHLW, the Japan Agency for Medical Research and Development (AMED) proceeded with Research Project on Development of Educational Programs for the Medical Practitioners who Engage in Interviews with Patients about Sensitive Matters as a research item from fiscal year 2016 to 2018.
AMED prepared educational materials that can be widely used in clinical settings for the purpose of enhancing medical communication skills of physicians and pharmacists involved in prescribing thalidomide. Such educational programs have rarely been developed in Japan. Specifically, the education program for the prescription of thalidomide is something that has not been established overseas either.

This time, a DVD was created as a drama with modeled interview scenes by physicians or pharmacists in medical consultations from the standpoint of medical psychology. It is strongly desired that the wide use of this educational material will contribute to thorough communication between healthcare professionals and patients and thereby result in prevention of effects on fetuses and best practices.

(source information provided only in Japanese)

Research Project on Development of Educational Programs for Healthcare Professionals who Engage in Interviews with Patients about Sensitive Matters (such as sexual intercourse or contraception)

Japan Agency for Medical Research and Development
Research on Regulatory Science of Pharmaceuticals and Medical Devices for fiscal year 2016-2018

Head of research and development
Kenshi Suzuki (Myeloma and Amyloidosis Center, Japanese Red Cross Medical Center)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated May 9, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Dulaglutide (genetical recombination)

Branded name (name of company)	Trulicity Subcutaneous Injection 0.75 mg Ateos (Eli Lilly Japan K.K.)
Therapeutic category	Hormones-miscellaneous
Indications	Type 2 diabetes mellitus

PRECAUTIONS (revised language is underlined)

[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Severe diarrhea, vomiting**: Cases of severe diarrhea and vomiting have also been reported that subsequently caused dehydration, leading to acute kidney injury.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	**Severe diarrhea, vomiting** Cases of severe diarrhea and vomiting have also been reported that subsequently caused dehydration, leading to acute kidney injury.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 32-month period (April 2016 to November 2018). Cases involving severe gastrointestinal disorder: 3 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 180 000 Japanese market launch: September 2015

Case summary

No.	Patient		Daily dose Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Type 2 diabetes mellitus (Decreased kidney function [creatinine 2.6], hypertension, hyperlipidemia, hyperuricemia, rheumatism)	0.75 mg/week For 50 days	**Abdominal pain** **Vomiting** **Dehydration** **Prerenal failure** Past history: unknown Allergy history/family history/prior medical intervention: unknown Past adverse reaction history: none Renal disease, renal vascular disease, collagen-vascular disease, nephrolithiasis, other vascular diseases (e.g. retinopathy): none Day 1 of administration: The patient was started on this drug 0.75 mg/week as an outpatient. 1 month after administration: The administration was continued with no complaints about adverse reactions at consultation. 50 days after administration (The day of discontinuation): The last administration of this drug 7 days after discontinuation (The day of occurrence): The patient experienced abdominal pain and vomiting. 12 days after discontinuation: The patient visited the emergency department. There were no findings indicating infections such as increased inflammatory reaction or fever. Since dehydration was observed, the patient was hospitalized and started on treatment with fluid replacement. Oral analgesics were administered too (details unknown). The patient was recovering from abdominal pain and vomiting, and dietary intake became favorable. Prerenal failure due to dehydration was observed (with an episode of rapidly decreased renal blood flow such as shock). Nocturia, lethargy or somnolence, myoclonus, edema, mental status changes, attack, sopor, other signs/symptoms: none 17 days after discontinuation: Fluid replacement and drinking water were ensured. Prerenal failure was recovering. The patient was discharged from the hospital since renal function improved. No rechallenge of this drug.

Laboratory Examination

	12 days after discontinuation	13 days after discontinuation	14 days after discontinuation	17 days after discontinuation
Norovirus antigen	(-)	-	-	-
Total protein (g/dL)	7.3	-	-	-
BUN (mg/dL)	65	-	65	42
Creatinine (mg/dL)	3.44	-	3.88	2.44
eGFR (mL/min/1.73 m^2)	15	-	13	22
Specific gravity urine	-	1.019	1.012	1.012
Urine protein (mg/day)	-	100	30	100
Urinary sugar	-	(-)	(-)	(-)
Urine ketone bodies	-	(-)	(-)	(-)
Urinary occult blood	-	(-)	(-)	(-)
Potassium (mEq/L)	4.2	-	3.9	4.3
Sodium (mEq/L)	134	-	135	137
Chlorine (mEq/L)	97	-	101	105
Calcium (mg/dL)	9.2	-	8.2	7.8
White blood cells (/μL)	10 500	8 900	10 100	9 000
CRP (mg/dL)	0.077	-	0.031	-

Concomitant therapies: diet therapy, exercise therapy
Concomitant medications: salazosulfapyridine, prednisolone insulin lispro, glimepiride, pioglitazone, losartan potassium/hydrochlorothiazide, febuxostat, cilnidipine, pitavastatin calcium

2 Empagliflozin

Branded name (name of company)	Jardiance Tablets 10 mg, 25 mg (Boehringer Ingelheim Japan, Inc.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (revised language us underlined)

[Under Old instructions] **Important Precautions**	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotizing fasciitis (Fournier's gangrene) of the external genitalia and perineum, and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse Reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotizing fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotizing fasciitis (Fournier's gangrene) of the external genitalia and perineum 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 taken.
[Under New instructions] **8. IMPORTANT PRECAUTIONS**	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis** Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), may occur, which may lead to sepsis (including septic shock).
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 35-month period (April 2016 to February 2019). Cases involving necrotizing fasciitis (Fournier's gangrene) of the external genitalia and perineum : 1 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 220 000. Japanese market launch: February 2015

Case summary

<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>1</td><td>Male
30s</td><td>Type 2 diabetes mellitus</td><td>10 mg
For 143 days</td><td>
Fournier's gangrene
Body height: approximately 170 cm, weight: approximately 80 kg
Past adverse reaction history: none
Drinking alcohol: none
Smoking: yes
Allergy: yes (alcohol)
Presence of neuropathy complicated with diabetes mellitus: no neuropathy, no neurogenic bladder
Medical consultation status, drug compliance, hygiene control: all favorable
Day 1 of administration: The patient was started on empagliflozin 10 mg, sitagliptin phosphate hydrate 50 mg, and glibenclamide 2.5 mg.
Day 20 of administration: The dose of glibenclamide was increased to 5 mg.
Day 142 of administration (Day of occurrence): Perineal pain developed.
Day 143 of administration (The day of discontinuation): The patient saw a nearby doctor, who referred him to this hospital. Inflammation was observed from the perineum to inguinal region. Body temperature was 38°C. CT scan suggested Fournier's gangrene. The primary infection foci were considered to be the region from the left perineum to inguinal region, and the scrotum. Emergency operation and drainage were performed. The patient was started on meropenem hydrate 3 g and clindamycin phosphate 1800 mg. Empagliflozin, sitagliptin phosphate hydrate, and glibenclamide were discontinued.
3 days after discontinuation: A culture test detected MRSA from the pus of the wound, which had been collected at day 143 of administration. The patient was started on vancomycin hydrochloride 2 g.
5 days after discontinuation: The patients recovered from tenderness and subjective symptoms improved.
9 days after discontinuation: The patient resumed receiving sitagliptin phosphate hydrate 50 mg.
13 days after discontinuation: The patient was started on metformin hydrochloride 500 mg.
33 days after discontinuation: Fournier's gangrene was recovering.

Laboratory Examination
<table>
<tr><th></th><th>Day 143 of administration</th><th>1 day after discontinuation</th><th>6 days after discontinuation</th><th>12 days after discontinuation</th><th>19 days after discontinuation</th></tr>
<tr><td>CRP(mg/dL)</td><td>4.05</td><td>13.15</td><td>0.13</td><td>0.13</td><td>0.04</td></tr>
<tr><td>WBC (10^3/μL)</td><td>21.7</td><td>17.0</td><td>11.5</td><td>11.5</td><td>9.5</td></tr>
<tr><td>HbA1c (%)</td><td>6.5</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td></tr>
<tr><td colspan="5">Concomitant medications: sitagliptin phosphate hydrate 50 mg, glibenclamide 2.5 mg or 5 mg</td></tr>
</table>

3 Nivolumab (genetical recombination)

Branded name (name of company)	Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Malignant melanoma Unresectable advanced or recurrent non-small cell lung cancer Unresectable or metastatic renal cell carcinoma Relapsed or refractory classical Hodgkin lymphoma Relapsed or metastatic head and neck cancer Unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy

PRECAUTIONS (revised language us underlined)

[Under Old instructions]

Important Precautions

Thyroid dysfunction, pituitary impairment and adrenal disorder may occur. Endocrine function test (measurement of TSH, free T3, free T4, ACTH, blood cortisol, etc.) should be performed prior to and periodically during administration of this drug. In addition, imaging assessment, etc. should be considered to perform as well when required. If any abnormalities are observed, appropriate measures should be taken.

Adverse Reactions (Clinically Significant Adverse Reactions)

Pituitary impairment:
Pituitary impairment such as hypophysitis, hypopituitarism, and adrenocorticotropic hormone deficiency may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Reference information

Number of cases (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 32-month period (April 2016 to November 2018).
Cases involving pituitary impairment: 11 (1 instance of patient mortality)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 17 000.

Japanese market launch: September 2014

Case summary

<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>1</td><td>Male
60s</td><td>Non-small cell lung cancer (with metastasis to lymph nodes, metastasis to lung, metastasis to skin, metastasis to peritoneum, anaemia, and smoking history)</td><td>3 mg/kg every 2 weeks, 7 times in total</td><td>Hypophysitis, erythema multiforme, abnormal hepatic function, increased C-reactive protein
Day 1 of administration: (First administration) Administration of nivolumab (3 mg/kg/day) was initiated for the treatment of unresectable, advanced or relapsed non-small cell lung cancer (histologic type: adenocarcinoma; treatment site: the left upper lobe; stage 4; TNM Classification: T4N3M1b; ALK fusion genes: negative; EGFR gene mutations: negative). The patient experienced malaise since the previous treatment, and complained of malaise even after the administration of nivolumab was initiated.
Day 64 of administration: Since the patient complained of malaise again at the time of visiting, dexamethasone was administered for treatment.
Day 88 of administration (seventh administration) (day of termination): Nivolumab was administered.
<u>14 days after termination</u>: The patient visited the hospital to receive nivolumab, with a fever of 38.5°C, poor oral intake, diarrhoea, and appetite impaired. At the medical consultation, hypotension, hypoglycaemia and hyponatraemia were observed, and adrenal insufficiency was suspected, and a detailed examination was performed. Since ACTH and cortisol level were decreased, nivolumab was discontinued. It was consulted with an endocrine internist, considering the effect that the patient did not take oral dexamethasone for a while that had been continuously administered before. Hypophysitis was suspected, and therefore, the patient started to receive hydrocortisone (15 mg) for treatment. Hydrocortisone sodium succinate (100 mg) injection was made for hypophysitis and increased serum CRP.
Date unknown: Head MRI revealed mild enlargement of the pituitary gland, and contrast MRI revealed slightly heterogeneous contrast image.
28 days after termination: The endocrine internist made a diagnosis of hypophysitis and adrenal insufficiency by the hypophysitis.
95 days after termination: Although hypophysitis improved after administration of steroids, there were sequelae (oral hydrocortisone was administered).</td></tr>
<tr><td></td><td colspan="4">Laboratory Examination
<table>
<tr><th></th><th><u>14 days after termination</u></th><th>25 days after termination</th><th>94 days after termination</th></tr>
<tr><td>ACTH (pg/mL)</td><td><1.0</td><td>-</td><td>-</td></tr>
<tr><td>Cortisol (μg/dL)</td><td>0.9</td><td>-</td><td>6</td></tr>
<tr><td>DHEA-S (μg/dL)</td><td>5</td><td>8</td><td>-</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant medications: none</td></tr>
</table>

Case summary

No.	Patient		Daily dose Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Non-small cell lung cancer (with lumbar disc herniation, gastric ulcer, metastasis to lymph nodes, pleural effusion, and smoking history)	3 mg/kg every 2 weeks, 24 times in total	**Hypophysitis, hypothyroidism, adrenocorticotropic hormone deficiency** Day 1 of administration: Administration of nivolumab (3 mg/kg/day) was initiated for the treatment of unresectable, advanced or relapsed non-small cell lung cancer (histologic type: squamous cell carcinoma; stage 4; TNM Classification: T3N3M1a). Day 434 of administration (22nd dose): Nivolumab was administered. Day 451 of administration: Hypophysitis was observed. A diagnosis of hypophysitis was made as a result of consultation with a physician specializing in endocrinology based on TSH increased to 20 μU/mL, FT4 decreased, ACTH decreased and GH decreased. Hydrocortisone was administered for treatment. Hypothyroidism (malaise), adrenal insufficiency symptoms (malaise, anorexia, nausea, vomiting, diarrhoea, hypotension, hyponatraemia, hypoglycaemia, weight decreased, consciousness disturbed and muscular weakness) were noted as clinical conditions. Day 455 of administration (23rd dose): Nivolumab was administered. Day 469 of administration (24th dose) (day of discontinuation): Nivolumab was administered. Decreased thyroid function was observed. The patient started to receive levothyroxine sodium hydrate (25 μg/day) for the treatment. Nivolumab was discontinued. 7 days after discontinuation: MRI was performed. Test results: no mass. CT/contrast CT was performed. No findings. 8 days after discontinuation: ACTH deficiency was observed. General malaise worsened. The patient could not eat and visited the emergency department. The patient was hospitalized for acute renal failure to treat decreased thyroid function and ACTH deficiency (vertigo as chief complaint, hyponatraemia, and increased eosinophil count). Hydrocortisone sodium succinate (100 mg/day) was administered for decreased thyroid function. The dosage of levothyroxine sodium hydrate was increased to 50 μg/day. 9 days after discontinuation: The patient started to receive oral hydrocortisone (25 mg/day). Subsequently, the symptom quickly improved but a polyuria trend and hyponatraemia persisted. Date unknown: A saline-loading test was performed for hyponatraemia. Urine sodium increased and hypouricemia persisted, and the patient responded well to NaCl load. Cerebral salt-wasting syndrome was suspected rather than syndrome inappropriate ADH (SIADH).

				12 days after discontinuation	The patient started to receive oral sodium chloride (1.5 g/day × 3). A rapid ACTH loading test was performed. [Findings] no reactions.
				15 days after discontinuation	A load test was performed using four hormones, GnRH (LH-RH) test and GRH test were performed. ACTH/F: unresponsive, GH: low reaction.
				16 days after discontinuation	The dosage of hydrocortisone acetate was reduced to 15 mg/day. MRI/contrast MRI was performed. [Findings] no enlargement of pituitary gland or mass
				17 days after discontinuation	A 5% hypertonic saline loading test was performed. The result was normal.
				22 days after discontinuation	The patient was discharged from the hospital.
				27 days after discontinuation	Hypophysitis resolved.
				30 days after discontinuation	ACTH deficiency and decreased thyroid function were recovering.

Laboratory Examination

	14 days before administration	Day 451 of administration	8 days after discontinuation	30 days after discontinuation
ACTH (pg/mL)	13.2	-	6.6	6.9
Cortisol (μg/dL)	9.5	-	0.7	1.2
Thyroid stimulating hormone (mU/L)	0.63	20	17.4	21.09

Concomitant medications: buprenorphine tape

4 Lenvatinib mesilate

Branded name (name of company)	Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	Unresectable thyroid cancer, unresectable hepatocellular carcinoma

PRECAUTIONS (revised language us underlined)

[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Interstitial lung disease**: Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 34-month period (April 2016 to January 2019). Cases involving interstitial lung disease: 5 (1 instance of patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 9 000. Japanese market launch: May 2015

Case summary

<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>1</td><td>Male
70s</td><td>Unresectable hepatocellular carcinoma (Type 2 diabetes mellitus, liver cirrhosis, arteriosclerosis, esophageal carcinoma)</td><td>12 mg
For 64 days
↓
Discontinued</td><td>Interstitial pneumonia
Weight: 62 kg
The patient had metastases to lymph nodes and a history of smoking.
2 days before administration: Chest CT scan findings: dorsal atelectasis in the bilateral lower lung lobes were detected. Funicular image in S5 of the bilateral lungs was observed, which was suggestive of a post-inflammation change. No nodular lesions suggestive of metastasis to the lung field were observed.
Day 1 of administration: The patient was started on lenvatinib mesilate 12 mg/day.
Day 64 of administration (The day of discontinuation): Drug-induced Interstitial pneumonia developed. It was detected by increased LDH and chest CT scan. A pulmonologist was consulted. Drug-induced Interstitial pneumonia was diagnosed because of elevated KL-6. (symptom: sputum).
Chest CT scan findings: Funicular image and ground-glass opacity became more intense at and around the peripheral regions of the bilateral lungs. Drug-induced pneumonia was suspected. No mass lesions in the lung field were observed. Plate-like hypertrophy and calcification at the pleura were observed. There was also a finding of pleural plaque. Neither enlargement of thoracic lymph nodes nor pleural effusion was observed.
35 days after discontinuation: The patient was started on oral prednisolone 30 mg.
103 days after discontinuation: The patient recovered from drug-induced Interstitial pneumonia.</td></tr>
<tr><td></td><td colspan="4">Laboratory Examination
<table>
<tr><th></th><th>3 days before administration</th><th>Day 64 of administration</th><th>4 days after discontinuation</th><th>21 days after discontinuation</th><th>35 days after discontinuation</th></tr>
<tr><td>KL-6 (U/mL)</td><td>-</td><td>-</td><td>817</td><td>865</td><td>740</td></tr>
<tr><td>SP-D (ng/mL)</td><td>-</td><td>-</td><td>334.5</td><td>193.8</td><td>-</td></tr>
<tr><td>LDH (IU/L)</td><td>192</td><td>280</td><td>-</td><td>231</td><td>183</td></tr>
<tr><td>CRP (mg/dL)</td><td>0.89</td><td>0.85</td><td>-</td><td>0.32</td><td>0.17</td></tr>
</table>
Concomitant medication: linagliptin</td></tr>
</table>

No.	Patient		Daily dose Treatment duration	**Adverse reactions**	
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Hepatocellular carcinoma (right hypochondrium pain)	8 mg For 10 days ↓ Discontinued	**Interstitial pneumonia** Weight: 56 kg The patient had metastases to lung. He was a smoker.	
				6 days before administration	Chest CT scan findings: multiple metastases to lung. Right pleural effusion (+), no interstitial shadows were observed.
				Day 1 of administration:	Lenvatinib mesilate 8 mg/day was initiated.
				Up to Day 9 of administration	Oxygen saturation was around 95 to 96% (room air).
				Day 10 of administration (The day of discontinuation)	Oxygen saturation dropped to 84% (room air) in the afternoon. The patient had no subjective symptoms at the time of the drop. Chest CT scan revealed bilateral interstitial shadows in the lung. The patient was diagnosed with drug-induced interstitial pneumonia. Oxygen inhalation started. Steroid pulse therapy was initiated (methylprednisolone sodium succinate 1 g for 3 days) SBT/ABPC 6 g/day started. Dyspnoea emerged. Chest CT scan findings: bilateral net-like shadows were observed (dominantly in the left lung). Sporadic elevations in concentration were newly noted. Similar or larger multiple metastases were observed compared with the previous scan. Right pleural effusion increased. Scarce left pleural effusion was noted.
				Day 11 of administration (day of discontinuation)	Oxygenation worsened. NPPV was applied. FiO2 was 50%. Administration of lenvatinib mesilate was discontinued.
				One day after discontinuation	Oxygenation worsened. NPPV was applied, FiO2 was 80 %. Disturbed consciousness emerged.
				2 days after discontinuation	The patient passed away form dyspnoea caused by drug-induced interstitial pneumonia.

Laboratory Examination

	6 days before administration	Day 8 of administration	Day 10 of administration	1 day after discontinuation	2 days after discontinuation
KL-6 (U/mL)	-	-	-		831
LDH (IU/L)	360	468	497	916	-
CRP (mg/dL)	11.69	14.28	19.09	13.27	-
β-D-glucan (pg/dL)	-	-	2.0	-	-

Concomitant medication: nifedipine, acetaminophen, loperamide hydrochloride, magnesium oxide

5 Influenza HA vaccine

Branded name (name of company)	Influenza HA Vaccine “Seiken” (Denka Seiken Co., Ltd.) Influenza HA Vaccine “KMB” (KM Biologics Co., Ltd.) Influenza HA Vaccine “Daiichi Sankyo” Syringe 0.25 mL and 0.5 mL, Influenza HA Vaccine “Daiichi Sankyo” 1 mL (Daiichi Sankyo Co., Ltd.) Flubik HA, and Flubik HA Syringe, Influenza HA Vaccine “Biken” (The Research Foundation for Microbial Diseases of Osaka University)
Therapeutic category	Vaccines
Indications	Prophylaxis of influenza

PRECAUTIONS (revised language us underlined)

[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalized exanthematous pustulosis**: Oculomucocutaneous syndrome and acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised examthematous pustulosis**
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported during the previous approximately 35-month period (April 2015 to February 2019). Cases involving acute generalized exanthematous pustulosis: 1 (no patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 50 000 000. Japanese market launch: September 1972

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th>Daily dose</th><th colspan="2">Adverse reactions</th></tr>
<tr><th>Sex/ Age</th><th>Reason for use (complications)</th><th>Treatment duration</th><th colspan="2">Clinical course and therapeutic measures</th></tr>
<tr><td>1</td><td>Female
90s</td><td>Influenza immunization
(type 2 diabetes mellitus, hypertension, uterine leiomyoma, colon cancer)</td><td>0.5 mL
Once</td><td colspan="2">Acute generalized exanthematous pustulosis
Date of vaccination: The patient received influenza HA vaccine (upper left arm).
2 days after vaccination: The patient experienced redness at the injection site and systemic rash. The patient was treated by a visiting physician with fexofenadine hydrochloride 120 mg, topical betamethasone valerate and gentamicin sulfate, and a drip infusion of stronger Neo-Minophagen C 20 mg.
8 days after vaccination: The patient had a fever, with body temperature in the 38 degrees Celsius range. Dermatology clinic A referred the patient to Hospital B, and the patient was admitted to the hospital on the same day.
At hospitalization, edematous erythema and miliary pustule accumulations were scattered around the trunk and extremities (especially around the site of vaccination at the upper left arm).
WBC: 20 230/μL, Neut: 85.1%, CRP: 10.3 mg/dL
The patient was started on topical diflorasone diacetate TID and oral epinastine hydrochloride 40 mg.
10 days after vaccination: WBC and Neut were improved to 18 080/μL and 84.6%, respectively.
Diflorasone diacetate was switched to difluprednate.
Skin rash gradually subsided.
16 days after vaccination: WBC: 6 320/μL, Neut: 70.5%, CRP: 1.3 mg/dL
The systemic condition was favorable.
17 days after vaccination: The patient was discharged from the hospital.</td></tr>
<tr><td></td><td colspan="5">Laboratory Examination
<table><tr><th></th><th>8 days after vaccination</th><th>9 days after vaccination</th><th>13 days after vaccination</th><th>23 days after vaccination</th><th>28 days after vaccination</th></tr><tr><td>CRP (mg/dL)</td><td>10.3</td><td>11.6</td><td>6.9</td><td>0.1</td><td>-</td></tr><tr><td>WBC (/μL)</td><td>20 230</td><td>16 240</td><td>15 490</td><td>4 880</td><td>-</td></tr><tr><td>Neut (/μL)</td><td>17 190</td><td>14 240</td><td>12 550</td><td>2 670</td><td>-</td></tr><tr><td>Lym (/μL)</td><td>1 830</td><td>1 080</td><td>2 020</td><td>1 830</td><td>-</td></tr><tr><td>DLST</td><td>-</td><td>-</td><td>-</td><td>-</td><td>Positive</td></tr></table></td></tr>
<tr><td></td><td colspan="5">Suspected concomitant medication: none
Concomitant drugs: trichlormethiazide, sarpogrelate hydrochloride, metformin hydrochloride, glimepiride, sitagliptin phosphate hydrate, valsartan, famotidine, pregabalin, magnesium oxide, etizolam, ambroxol hydrochloride</td></tr>
</table>

4

Revision of Precautions (No.303)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated May 9, 2019.

1 Hormones-miscellaneous

Dulaglutide (genetical recombination)

Branded name	Trulicity Subcutaneous Injection 0.75 mg Ateos (Eli Lilly Japan K.K.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions)	**Severe diarrhoea, vomiting**: Cases with severe diarrhoea and vomiting have also been reported that subsequently caused dehydration, leading to acute kidney injury.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	**Severe diarrhoea, vomiting** Cases with severe diarrhoea and vomiting have also been reported that subsequently caused dehydration, leading to acute kidney injury.

2 Antidiabetic agents

a. Ipragliflozin L-proline
b. Tofogliflozin hydrate

Branded name	a. Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc. b. Apleway Tablets 20 mg (Sanofi K.K.), Deberza Tablets 20 mg (Kowa Company, Ltd.)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gan-

	grene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis** Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

3 **Antidiabetic agents**

Empagliflozin

Branded name	Jardiance Tablets 10 mg, 25 mg (Boehringer Ingelheim Japan, Inc.)
[Under Old instructions] **Important Precautions**	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.
[Under New instructions] **8. IMPORTANT PRECAUTIONS**	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis** Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

4 **Antidiabetic agents**

Empagliflozin/linagliptin

Branded name	Tradiance Combination Tablets AP, BP (Boehringer Ingelheim Japan, Inc.)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur by administration of empagliflozin, an ingredient of this drug, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.

5 **Antidiabetic agents**

Canagliflozin hydrate

Branded name	Canaglu Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**

11.1 Clinically Significant Adverse Reactions	Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

6 **Antidiabetic agents**

Sitagliptin phosphate hydrate/ipragliflozin L-proline

Branded name	Sujanu Combination Tablets (MSD K.K.)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur by administration of ipragliflozin, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Urinary tract infection and genital infection may occur by ipragliflozin, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**
11.1 Clinically Significant Adverse Reactions	Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

7 **Antidiabetic agents**

Dapagliflozin propylene glycolate hydrate

Branded name	Forxiga Tablets 5 mg, 10 mg (AstraZeneca K.K.)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**
11.1 Clinically Significant Adverse Reactions	Pyelonephritis and necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

8 **Antidiabetic agents**

Teneligliptin hydrobromide hydrate/canagliflozin hydrate

Branded name	Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur by administration of canagliflozin, an active ingredient of this drug, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock). Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken such as discontinuation of administration.
[Under New instructions]	

8. IMPORTANT PRECAUTIONS	Urinary tract infection and genital infection may occur by administration of canagliflozin, an active ingredient of this drug, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**
11.1 Clinically Significant Adverse Reactions	Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

9 **Antidiabetic agents**

Luseogliflozin hydrate

Branded name	Lusefi tab. 2.5 mg, 5 mg (Taisho Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Important Precautions	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**: Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) 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 taken.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Urinary tract infection and genital infection may occur, which may lead to serious infections such as pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), and sepsis. Patients should be carefully monitored for urinary tract infection and genital infection. If such infections occur, appropriate measures should be taken, and measures such as temporary discontinuation of this drug should be considered based on the patient's condition. Symptoms and management of urinary tract infection and genital infection should be explained to patients.
11. ADVERSE REACTIONS	**Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene), sepsis**
11.1 Clinically Significant Adverse Reactions	Pyelonephritis, necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) may occur, which may lead to sepsis (including septic shock).

10 **Antineoplastics-miscellaneous**

Nivolumab (genetical recombination)

Branded name	Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Important Precautions	Thyroid dysfunction, pituitary impairment and adrenal disorder may occur. Endocrine function test (measurement of TSH, free T3, free T4, ACTH, blood cortisol, etc.) should be performed prior to and periodically during administration of this drug. In addition, imaging assessment, etc. should be considered to perform as well when required. If any abnormalities are observed, appropriate measures should be taken.
Adverse reactions (Clinically Significant Adverse Reactions)	**Pituitary impairment**: Pituitary impairment such as hypophysitis, hypopituitarism, and adrenocorticotropic hormone deficiency may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

11 **Antineoplastics-miscellaneous**

Lenvatinib mesilate

Branded name	Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.)
[Under Old instructions]	
Adverse reactions (Clinically Significant Adverse Reactions)	**Interstitial lung disease**: Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

12 **Vaccines**

Influenza HA vaccine

Branded name	Influenza HA Vaccine “Seiken” (Denka Seiken Co., Ltd.) Influenza HA Vaccine “KMB” (KM Biologics Co., Ltd.) Influenza HA Vaccine “Daiichi Sankyo” Syringe 0.25 mL and 0.5 mL, Influenza HA Vaccine “Daiichi Sankyo” 1 mL (Daiichi Sankyo Co., Ltd.) Flubik HA, and Flubik HA Syringe, Influenza HA Vaccine “Biken HA” (The Research Foundation for Microbial Diseases of Osaka University)
[Under Old instructions]	
Adverse reactions (Clinically Significant Adverse Reactions)	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised examthematous pustulosis**: Oculomucocutaneous syndrome and acute generalised examthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised examthematous pustulosis**

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 newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 30 April, 2019)
◎: Products for which EPPV was initiated after April 1, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate Biktarvy Combination Tablets	Gilead Sciences Inc.	April 8, 2019
	Tafamidis meglumine*1 Vyndaqel capsules 20 mg	Pfizer Japan Inc.	March 26, 2019
	Landiolol hydrochloride*2 Onoact for Intravenous Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	March 26, 2019
	Dupilumab (genetical recombination) *3 Dupixent Subcutaneous Injection 300 mg Syringe	Sanofi K.K.	March 26, 2019
	Dapagliflozin propylene glycolate hydrate*4 Forxiga Tablets 5 mg, 10 mg	AstraZeneca K.K.	March 26, 2019
	Nalmefene hydrochloride hydrate Selincro tablets 10 mg	Otsuka Pharmaceutical Co., Ltd	Match 5, 2019
	Romosozumab (genetical recombination) Evenity subcutaneous injection 105 mg syringe	Amgen Astellas BioPharma K.K.	March 4, 2019
	Dacomitinib Hydrate Vizimpro Tablets 15 mg, 45 mg	Pfizer Japan Inc.	March 1, 2019
	Relugolix Relumina Tablets 40 mg	Takeda Pharmaceutical Company Limited.	March 1, 2019
	Lorazepam Lora-pita Intravenous Injection 2mg	Pfizer Japan Inc.	March 1, 2019
	Binimetinib Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
	Encorafenib Braftovi Capsules 50 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019
	Sofosbuvir/velpatasvir Epclusa Combination Tablets	Gilead Sciences Inc.	February 26, 2019
	Metirosine Demser Capsules 250 mg	Ono Pharmaceutical Co., Ltd.	February 26, 2019

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Damoctocog alfa pegol (genetical recombination) Jivi for i.v. injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin Ltd	February 12, 2019
Secukinumab (genetical recombination) *1 Cosentyx for s.c. injection 150 mg syringe	Novartis Pharma K.K.	December 21, 2018
Ipragliflozin L–proline *2 Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	December 21 2018
Dolutegravir sodium/rilpivirine hydrochloride Juluca Combination Tablets	Viiv Healthcare K.K.	December 20, 2018
Gilteritinib fumarate Xospata Tablets 40 mg	Astellas Pharma Inc.	December 3, 2018
Abemaciclib Verzenio Tablets 50 mg, 100 mg, 150 mg	Eli Lilly Japan K.K.	November 30, 2018
Dexmedetomidine hydrochloride a. Precedex Intravenous Solution 200 μg [Pfizer], b. Precedex Intravenous Solution 200 μg/50 mL syringe [Pfizer], c. Precedex Intravenous Solution 200 μg [Maruishi], d. Precedex Intravenous Solution 200 μg/50 mL syringe [Maruishi]	a, b Pfizer Japan Inc. c, d Maruishi Pharmaceutical Co., Ltd.	November 29, 2018
Macrogol 4000/sodium chloride/sodium bicarbonate/potassium chloride Movicol Combination Powder	EA Pharma Co., Ltd.	November 29, 2018
Omidenepag isopropyl Eybelis Ophthalmic Solution 0.002%	Santen Pharmaceutical Co., Ltd.	November 27, 2018
Vibegron Beova Tablets 50 mg	Kyorin Pharmaceutical Co.,Ltd.	November 27, 2018
Blinatumomab (genetical recombination) Blincyto I.V. Infusion 35 μg	Amgen Astellas BioPharma K.K.	November 27, 2018
Lorlatinib Lorbrena Tablets 25 mg, 100 mg	Pfizer Japan Inc.	November 20, 2018
Icatibant acetate Firazyr subcutaneous injection 30 mg syringe	Shire Japan KK	November 20, 2018
Vedolizumab (genetical recombination) Entyvio for I.V. Infusion 300 mg	Takeda Pharmaceutical Company Limited.	November 7, 2018
Nonacog beta pegol (genetical recombination) Refixia I.V. Injection 500, 1000, 2000	Novo Nordisk Pharma Ltd.	November 1, 2018

*1 Transthyretin cardiac amyloidosis (wild type and mutant type)

*2 The following life-threatening arrhythmias when they are refractory and time-critical
Ventricular fibrillation, ventricular tachycardia accompanied by haemodynamic instability

*3 Bronchial asthma (only for sever or refractory cases whose symptoms are not adequately controlled with existing treatments)

*4 Type 1 diabetes mellitus

*5 Ankylosing spondylitis that does not adequately respond to existing treatments