Pharmaceuticals and Medical Devices Safety Information

No. 407 February 2024

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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) web page (https://www.pmda.go.jp/english/) and on the MHLW website (https://www.mhlw.go.jp/, only available in Japanese language).

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 the MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

Register here

Published by
Ministry of Health, Labour and Welfare

Pharmaceutical Safety Division,

Translated by
Pharmaceuticals and Medical Devices Agency

Pharmaceuticals and Medical Devices Agency

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Pharmaceuticals and Medical Devices Safety Information

No. 407 February 2024

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

[Outline of Information]

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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 healthcare professionals.

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)

https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HSB	Health Service Bureau
IVC	Inferior Vena Cava
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SOC	System Organ Class

1
Suspected Adverse Reactions to Influenza Vaccines in the 2022 Season

1. Introduction

This section describes the status of instances of suspected adverse reactions to influenza vaccines reported from October 1, 2022 through March 31, 2023 (hereinafter referred to as the "2022 season").

Medical institutions are required to report to the MHLW when they encounter symptoms from influenza vaccines that they decide meet the Suspected Adverse Reaction Reporting Criteria regardless of causality. Reports by medical institutions, together with those by the MAHs, are compiled and evaluated by the PMDA. For serious cases, including fatal cases, the PMDA performs causality assessment and/or considers the necessity of safety measures in consultation with experts.

Joint meetings of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as the "Joint Meeting") are convened periodically for the purpose of investigating and reviewing these reports of suspected adverse reactions to influenza vaccines and to discuss the necessity of safety measures[1)].

2. Reports of suspected adverse reactions to influenza vaccines (2022 season)

(1) Numbers and frequencies of suspected adverse reactions reported

Table 1 shows the numbers of reported suspected adverse reactions to the influenza vaccines and frequencies calculated from the estimated numbers of vaccinated persons based on the number of vaccines distributed to medical institutions.

Table 1 Numbers of suspected adverse reactions reported and estimated number of vaccinated persons

	Reports by MAHs (serious reports)*		Reports by medical institutions**		
Estimated number of vaccinated persons (number of vaccinations)	Number of serious cases reported (frequency)	Number of patient mortalities reported	Number of reports (frequency)	Number of serious cases reported (frequency)	Number of patient mortalities reported
51 451 020 (as of March 31, 2023)	17 (0.000033%)	0 (0%)	71 (0.00014%)	33 (0.00006%)	5 (0.0000097%)

* Reports by the MAHs were on cases determined to be "serious" under Article 68-10, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act). Reports by the MAHs may duplicate some cases reported by medical institutions, and such duplicated cases are included in the number for reports by medical institutions.

** Reports by medical institutions were submitted under Article 12, Paragraph 1 of the Preventive Vaccination Law (PV Law) or Article 68-10, Paragraph 2 of the PMD Act.

(2) Reports of suspected adverse reactions by sex and age group

The numbers of reported suspected adverse reactions to influenza vaccines are shown by sex and age group in Table 2 and Table 3, respectively.

Table 2 Number of reports by sex

Sex	Number of Reports by MAHs (serious cases)	Number of reports by medical institutions
Male	9	32
Female	8	39
Unknown	0	0
Total	17	71

Table 3 Number of reports by age group

Age group	Number of Reports by MAHs		Number of reports by medical institutions		
	Number of serious cases reported		Number of reports	Number of serious cases reported	
		Number of patient mortalities reported			Number of patient mortalities reported
0 - 9	3	0	24	12	0
10 - 19	3	0	7	2	0
20 - 29	2	0	2	2	0
30 - 39	1	0	1	0	0
40 - 49	0	0	4	1	0
50 - 59	0	0	4	1	0
60 - 69	2	0	5	5	0
70 - 79	3	0	14	6	3
80 or older	2	0	10	4	2
Unknown	1	0	0	0	0
Total	17	0	71	33	5

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported during the 2022 season are outlined by System Organ Class (SOC) in the right-hand side columns of Table 4. There were no increases in the numbers and frequencies of adverse reactions reported compared with the 2021 season (October 1, 2021 to September 30, 2022).

A total of 5 cases of post-vaccination deaths were reported for this season. The assessment by experts determined that the causality between the vaccination and death could not be assessed due to lack of information for these cases.

A total of 6 cases Note 1) of possible Guillain-Barré syndrome or acute disseminated encephalomyelitis (ADEM) were reported for this season. The assessment by experts determined that a causal relationship between the respective diseases and vaccination was reasonably possible for 2 cases.

A total of 8 cases Note 2) were reported as possible anaphylaxis. Experts concluded that none of the cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria. Regarding the number of reports from the MAHs by manufacturing lot, no distinct increases in the number of cases reported as possible anaphylaxis were attributed to any of the specific lots.

At the Joint Meeting held in July 2023, it was concluded that there were no new concerns regarding the safety of the vaccines, including other reported symptoms than anaphylaxis, with no safety measures such as revision of package inserts required at present, but reporting of

suspected adverse reactions and their details should be carefully monitored.

Note 1) Cases reported with the symptom name “Guillain-Barré syndrome” or “ADEM”
Note 2) Cases reported with the symptom name “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” or “anaphylactoid shock.”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2021 and 2022 seasons (by SOC)

	2021 season†		2022 season††	
SOC of symptom	Reports by MAHs (serious cases)	Reports by medical institutions (serious cases)	Reports by MAHs (serious cases)	Reports by medical institutions (serious cases)
Gastrointestinal disorders	1	7	3	7
General disorders and administration site conditions	8	19	8	11
Infections and infestations	1	7	0	7
Haepatobiliary disorders	5	2	0	1
Eye disorders	1	0	2	0
Musculoskeletal and connective tissue disorders	1	5	1	4
Blood and lymphatic system disorders	1	3	0	4
Vascular disorders	1	1	0	5
Respiratory, thoracic and mediastinal disorders	2	6	1	8
Injury, poisoning and procedural complications	0	0	0	1
Cardiac disorders	2	2	0	2
Nervous system disorder	6	16	5	23
Renal and urinary disorders	8	7	2	1
Mental disorder	0	0	0	1
Metabolic and nutritional disorders	1	0	0	3
Endocrine disorders	0	0	0	1
Skin and subcutaneous tissue disorders	5	3	2	3
Immune system disorders	2	8	4	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1
Investigations	5	2	0	3
Total	50	88	28	91

† Reported from October 1, 2021 to September 30, 2022
†† Reported from October 1, 2022 to March 31, 2023

3. Future safety measures

As detailed in the “Reporting Suspected Adverse Reactions for Routine Vaccination, etc.” notification[2)], medical institutions are urged to promptly report when they encounter symptoms that they believe meet the Suspected Adverse Reaction Reporting Criteria even if the causality is

unclear.

In addition to the conventional reporting by fax, electronic reporting is available through the website since April 1, 2021.

[Report Reception Site (electronic report system)]

https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)

The MHLW/PMDA will continue their efforts to gather information concerning the safety of influenza vaccines including suspected adverse reaction reports, etc. and to implement safety measures based on such information. Continued cooperation is requested in alerting vaccine recipients to adverse reactions and reporting them when suspected.

[References]

1) MHLW: The Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 94th meeting) and the 2023 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 5th meeting) (Joint Meeting)
   ・Material 2-26 Reports of Suspected Adverse Reactions to Influenza Vaccines
   https://www.mhlw.go.jp/content/10601000/001126218.pdf (only in Japanese)
   ・Material 2-31 List of reports of fatal cases after vaccination
   https://www.mhlw.go.jp/content/10601000/001126224.pdf (only in Japanese)

2) "Partial Amendment of Reporting Suspected Adverse Reactions for Routine Vaccinations, etc." dated March 31, 2023, Joint HSB Notification No. 0331-16 and PSEHB Notification No.0331-5, by the Director-General of Health Service Bureau and by the Director-General of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labor and Welfare
   https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/kanrentuuti.html (only in Japanese)

   Report form
   https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r04youshiki_02.pdf (only in Japanese)

   Entry instructions
   https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r04youshiki_03.pdf (only in Japanese)

   Report entry application (National Institute of Infectious Diseases)
   http://www.nih.go.jp/niid/ja/vaccine-j/6366-vaers-app.html (only in Japanese)

Reference: Suspected Adverse Reaction Reporting Criteria
<Routine vaccination>

Symptoms	Time to onset after inoculation
Anaphylaxis	4 hours
Hepatic impairment	28 days
Interstitial pneumonia	28 days
Acute disseminated encephalomyelitis (ADEM)	28 days
Acute generalised exanthematous pustulosis (AGEP)	28 days
Guillain-Barré syndrome	28 days
Convulsion	7 days
Vasculitis	28 days
Thrombocytopenic purpura	28 days
Optic neuritis	28 days
Myelitis	28 days
Asthmatic attack	24 hours
Nephrotic syndrome	28 days
Encephalitis or encephalopathy	28 days
Oculomucocutaneous syndrome	28 days
Other reactions (symptoms suspected to be associated with the vaccination and either (1) requiring hospital admission or (2) resulting in, or associated with a risk of death or persistent incapacity)	Time frame in which the event was considered by the physician to be associated with the vaccination

Except for “other reactions,” any event occurring within the specified time frame is subject to mandatory reporting to the MHLW regardless of causality under the PV Law and related rules.

<Voluntary vaccination>

Adverse reactions or infections associated with voluntary vaccinations should be reported when reporting is considered necessary to prevent the occurrence and spread of health hazards. Refer to the following for specific cases subject to reporting. Adverse reactions and infections for which causality with vaccinations is unclear may also be subject to reporting.

(1) Death
(2) Disability
(3) Events that may result in death
(4) Events that may result in disability
(5) Symptoms that require admission or prolonged hospitalization at medical institutions for treatment [excluding events in (3) and (4)]
(6) Serious events corresponding to those in items (1) to (5)
(7) Congenital diseases or anomalies in the next generation
(8) Onset of infections suspected of being caused by use of the applicable pharmaceutical
(9) Onset of unknown events which are not mild and could not be predicted based on the package insert, other than those listed in (1) to (8)

2
The Manuals for Management of Individual Serious Adverse Drug Reactions

1. Introduction

Conventional safety measures implemented in Japan had been drug-oriented and mainly “alert-issue” and “post-event response” types, i.e., information of adverse drug reactions (ADRs) was collected and evaluated for each drug and notified to the clinical settings. However, these types of measures may not be, occasionally, effective enough for early detection of ADRs, leading to serious conditions, for example, for the following reasons:
(1) ADRs may occur in the organs in which clinicians are not specialized.
(2) The incidence of serious ADRs is generally low, and some clinicians may have little experience with such events.

Therefore, the MHLW has implemented the “Project of Comprehensive Measures for Serious ADRs” (hereinafter referred to as the "Project," the Project has been ongoing as the “Development Project of the Manuals for Management of Individual Serious ADRs” since FY 2021.) since 2005 in order to develop safety measures that “predict” and “prevent” ADRs, focusing on diseases caused by the use of drugs, in addition to conventional drug-oriented ADR safety measures, and to promote research to elucidate the mechanism of ADRs, etc.

In this project, “The Manuals for Management of Individual Serious ADRs” (hereinafter referred to as the "Manuals") were compiled from FY 2005 to FY 2010 by the Committee on the Comprehensive Actions for Serious ADRs who reviewed and compiled the drafts prepared by the Manual preparation committees organized in related academic societies through discussion with the Japanese Society of Hospital Pharmacists (JSHP) as entrusted by the MHLW in this project. The drafts were prepared with reference to academic papers, various guidelines, health and labour science research project reports, PMDA health and welfare service reports, etc.

In order to promote further utilization of the Manuals after a certain period of time has elapsed since its compilation, revisions based on the latest knowledge have been made over the five years since FY 2016, with the cooperation of related academic societies and others. In addition, we continue to revise the Manuals and prepare new ones as necessary, and promote them to the general public.

2. Progress of revisions, etc.

In FY 2022, we revised or newly drafted the following Manuals. The revisions were reported and discussed at the meeting of the Committee on the Comprehensive Actions for Serious ADRs held on September 20, 2023 and were published in December 2023.

Author	Manual title	Category: New (newly prepared) or Revision
The Japanese Circulation Society	Severe hypertension	New
The Japan Diabetes Society	Hyperglycemia	Revision
	Hypoglycemia	Revision

The Manuals published this time, following the Manuals published last year, include explanations about relief for sufferers of ADRs at the end of the section “About this Manual” in the beginning of each Manual. The Manuals also provide the number of payments for relief benefits in the past 5 years under the Relief System for ADRs and information concerning the Relief System for ADRs at the end of each Manual.

3. Plans for further revisions, etc.

In FY 2023, draft revisions of the following Manuals are being prepared based on the opinions of the Committee and the academic societies. The Manuals are scheduled to be published after being reported and discussed at the Committee on the Comprehensive Actions for Serious ADRs.

Author	Manual title	Category: New (newly prepared) or Revision
Japanese Society of Oral and Maxillofacial Surgeons	Antiresorptive agents-related osteonecrosis/osteomyelitis of the jaws (ARONJ)	Revision
Japanese Society of Nephrology	Nephrotic syndrome	Revision
	Vasculitis (antineutrophil cytoplasmic antibody associated angiitis)	Revision

4. Increasing awareness of the Manuals

In order to further disseminate the Manuals and to promote early detection and treatment of serious ADRs, we have been working on awareness-raising initiatives of the Manuals since FY 2021.

In December 2023, we prepared a poster introducing the Manual of “severe hypertension” which was newly compiled. The electronic version of the poster can be found on the MHLW and PMDA website.
(https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html, https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html) (only in Japanese).

An educational video, etc. for patients and their families about the Manuals prepared and published by FY 2022 is also available via the link above. You are encouraged to watch the video.

重症高血圧のマニュアルが新規作成されました！

重篤副作用疾患別対応マニュアルには、自覚症状などから重大な副作用を早期に発見できるような患者及び家族の方向けの情報や、医療関係者向けの診断方法及び対処方法などが記載されています。

重篤副作用疾患別対応マニュアル

- ▶早期発見と早期対応のポイント
- ▶副作用の判別基準
- ▶判別が必要な疾患と判別方法
- ▶治療方法
- ▶典型的症例概要

例えば、重症高血圧のマニュアルなら…

- 臓器障害を伴わない限り、多くの場合無症状
- 処方されている薬の中で、高血圧のリスクとなる薬を把握することが必要

普段から家庭で血圧を測り、自分の血圧を知っておくことが重要です。ご心配な点は気軽に薬剤師にお聞き下さい。

重篤副作用疾患別対応マニュアルを日常業務で使ってみよう！

重篤副作用疾患別対応マニュアルは、こちらのQRコードからご覧いただけます。

厚生労働省 ひと、くらし、みらいのために Ministry of Health, Labour and Welfare

一般社団法人 日本循環器学会

5. Closing remark

Healthcare professionals are requested to continue to cooperate in the proper use of drugs by utilizing the Manuals and informing patients of them as necessary. The Manuals are available on the MHLW and PMDA websites.

[References]

MHLW website “Manuals for Management of Individual Serious ADRs”
(https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html) (only in Japanese)

PMDA website “Manuals for Management of Individual Serious ADRs” (intended for healthcare professionals)
(https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html) (only in Japanese)

Previous articles introducing the Initiative of Revision of the Manuals for Management of Individual Serious ADRs

1. Pharmaceuticals and Medical Devices Safety Information No.348
   (https://www.pmda.go.jp/files/000221054.pdf)
2. Pharmaceuticals and Medical Devices Safety Information No.357
   (https://www.pmda.go.jp/files/000226311.pdf)
3. Pharmaceuticals and Medical Devices Safety Information No.368
   (https://www.pmda.go.jp/files/000232763.pdf)

The Manuals for Management of Individual Serious ADRs: Pharmaceuticals and Medical Devices Safety Information No.393
(https://www.pmda.go.jp/files/000247416.pdf)

The Manuals for Management of Individual Serious ADRs: Pharmaceuticals and Medical Devices Safety Information No.402
(https://www.pmda.go.jp/files/000263297.pdf)

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated January 10, 2024, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 [1] Acetazolamide
[2] Acetazolamide sodium

Brand name (name of company)	[1] Diamox Powder, Diamox Tablets 250 mg (Sanwa Kagaku Kenkyusho Co., Ltd.) [2] Diamox for Injection 500 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
Therapeutic category	Diuretics
Indications	[1] (Powder) Glaucoma, epilepsy (to be added when other antiepileptics are not sufficiently effective), improvement of respiratory acidosis in emphysema, cardiac induced oedema, hepatic induced oedema, premenstrual tension, Meniere's disease and syndrome (Tablets) Glaucoma, epilepsy (to be added when other antiepileptics are not sufficiently effective), improvement of respiratory acidosis in emphysema, cardiac induced oedema, hepatic induced oedema, premenstrual tension, Meniere's disease and syndrome, sleep apnoea syndrome [2] Glaucoma, epilepsy (to be added when other antiepileptics are not sufficiently effective), improvement of respiratory acidosis in emphysema, Meniere's disease and syndrome

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	<u>Acute respiratory distress syndrome, pulmonary oedema</u> <u>If rapidly progressive dyspnoea, hypoxaemia, or chest X-ray abnormalities such as diffuse infiltrative shadow in both lungs are observed, administration of this drug should be discontinued, and appropriate measures should be taken.</u>
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports and retrieved for adverse reactions name (PT) "acute respiratory distress syndrome," "acute pulmonary oedema," "pulmonary oedema," and "non-cardiogenic pulmonary oedema" Considering possibilities such as assessment of acute respiratory distress syndrome being difficult due to lack of diagnostic information but assessment of pulmonary oedema being possible in some of the cases, a causality assessment of the retrieved cases was conducted as "acute respiratory distress syndrome" and "pulmonary oedema," respectively.

Cases involving acute respiratory distress syndrome reported in Japan:
[1] 2 (No patient mortalities)
[2] 7 cases, including 6 cases in which the drug was administered outside the approved indications (No patient mortalities)
Cases involving acute respiratory distress syndrome reported overseas:
[1] 4 cases, including 1 case which fell under the contraindications (No patient mortalities)
[2] 0

Cases involving pulmonary oedema reported in Japan:
[1] 2 (No patient mortalities)
[2] 7 cases, including 6 cases in which the drug was administered outside the approved indications (No patient mortalities)
Cases involving pulmonary oedema reported overseas:
[1] 4 cases, including 1 case which fell under the contraindications (No patient mortalities)
[2] 0

Number of patients using the drug as estimated by the MAH during the previous 1-year period:
[1] Diamox Powder: Approximately 1 279, Diamox Tablets: approximately 186 440
[2] Diamox for Injection: approximately 18 724
Japanese market launch:
[1] Diamox Powder: August 1958, Diamox Tablets: March 1955
[2] Diamox for Injection: December 1963

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 80s	Normal tension glaucoma (hyperkalaemia)	250 mg for 1 day	**Pulmonary oedema**	
				1 day before administration	No abnormalities were noted in the patient's condition.
				Day 1 of administration (day of discontinuation)	At around 10 o'clock in the morning, the patient took 1 tablet of acetazolamide for normal tension glaucoma. After 1 hour, symptoms of pulmonary oedema (dyspnoea) developed. The patient was transported by ambulance due to respiratory failure. A culture test detected only highly susceptible *Staphylococcus aureus* from the sputum, and others were negative. In addition, the result of an antigen test of *Streptococcus pneumoniae* and *Legionella*, various fungal tests, and auto-antibody tests were negative. At the ICU, the patient underwent tracheal intubation and was kept under artificial respiratory management. ECG (before 2 o'clock): Heart rate 132 bpm, PR interval 178 ms, QRS width 94 ms, QT/QTc (E) interval 326/404 ms, P/QRS/T axis 270/92/64, RV5/SV1 value 0.63/0.69mV, RV5+SV1 value 1.32mV. Tachycardiac atrial rhythm (sinus tachycardia (no measures were taken for sinus tachycardia)), non-specific abnormal T-wave, slight right-axis deviation, suspicion of pulmonary disease, abnormal ECG. Minnesota Code 2-3 9-4-2. Echocardiographic findings (4 o'clock in the afternoon): Inferior vena cava (IVC) was 14 mm, showing a slight improvement. However, collapse of the cardiac chamber occurred. Echocardiographic findings (7 o'clock in the evening): In spite of tachycardia where the heart rate was in the 120s, no respiratory variation was noted in IVC. Blood flow into the left ventricular chamber was limited. Chest X-ray findings: Right-side dominant bilateral infiltrative shadow was noted.
				1 day after discontinuation	Furosemide was used as a diuretic. Administration of meropenem hydrate was initiated due to increased CRP (CRP 18.59 mg/dL). Echocardiographic findings: Heart rate in the 130s, BP around 130/70. Respiratory variation of SpO_2 was marked on the monitor. Left ventricular hypokinesis was noted. IVC was 10 mm. Kissing sign was noted. At around 11 o'clock in the evening, lateral decubitus position was completed. Echocardiographic assessment was performed again: Left ventricular hypokinesis was noted; respiratory variation was 80% or more in IVC. Chest X-ray findings: Right-side dominant bilateral infiltrative shadow was noted. Permeability improved compared to the previous day.
				2 days after discontinuation	Chest X-ray findings: Permeability slightly improved. Bilateral pleural effusions were noted.

				3 days after discontinuation	Chest X-ray findings: Infiltrative shadow of the right lower lung field remained.
				4 days after discontinuation	Chest X-ray findings: Infiltrative shadow in bilateral lungs improved.
				5 days after discontinuation	Chest X-ray findings: Bilateral pleural effusions increased, and permeability decreased.
				6 days after discontinuation	Respiratory conditions tended to improve. Decannulation was considered. Administration of meropenem hydrate was completed. Chest X-ray findings: No change was noted compared to the previous day.
				7 days after discontinuation	Extubation was performed. Chest X-ray findings: Bilateral permeability slightly improved. Infiltrative shadow further improved.
				8 days after discontinuation	Chest X-ray findings: Permeability in bilateral lungs improved.
				9 days after discontinuation	The patient left the ICU and began to eat meals. Chest X-ray findings: No change was noted compared to the previous time.
				12 days after discontinuation	Chest X-ray findings: Permeability in bilateral lungs improved.
				15 days after discontinuation	The patient's respiratory condition stabilized.
				17 days after discontinuation	Chest X-ray findings: Permeability in bilateral lungs further improved, and pneumatization increased.
				19 days after discontinuation	Chest X-ray findings: No change was noted compared to the previous time.
				20 days after discontinuation	Pulmonary oedema was resolving. The patient was discharged from the hospital.

Laboratory test value

	Day 1 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation	6 days after discontinuation	19 days after discontinuation
WBC (cells/μL)	3 160	16 640	10 620	4 440	6 430	4 580	6 150	4 510
CRP (mg/dL)	0.51	18.59	12.17	5.24	1.83	0.76	0.46	1.39
Cre (mg/dL)	1.24	2.08	1.72	1.17	—	—	0.65	0.71
NT-proBNP (pg/mL)	189	1 830	—	393	—	—	—	

Concomitant drugs: Esomeprazole magnesium hydrate, rebamipide, limaprost alfadex, benzbromarone, allopurinol, furosemide, ethyl icosapentate, tocopherol nicotinate, cilostazol, keishikaryukotsuboreito, carteolol hydrochloride/latanoprost, brimonidine tartrate/brinzolamide, ketoprofen

2 •Dexamethasone preparations [1] Dexamethasone (oral dosage form), [2] Dexamethasone palmitate, [3] Dexamethasone sodium phosphate (injections), •Prednisolone preparations [1] Prednisolone (oral dosage form), [2] Prednisolone sodium succinate, [3] Prednisolone sodium phosphate •Methylprednisolone preparations [1] Methylprednisolone, [2] Methylprednisolone sodium succinate, [3] Methylprednisolone acetate •Cortisone/hydrocortisone preparations [1] Cortisone acetate, [2] Hydrocortisone, [3] Hydrocortisone sodium succinate (preparations indicated for lymphoid tumours), [4] Hydrocortisone sodium succinate (preparations not indicated for lymphoid tumours), [5] Hydrocortisone sodium phosphate

Brand name (name of company)	•Dexamethasone preparations [1] Decadron Tablets 0.5 mg, 4 mg (Nichi-Iko Pharmaceutical Co., Ltd.) [1] Decadron Elixir 0.01% (Nichi-Iko Pharmaceutical Co., Ltd.), and the others [1] LenaDex Tablets 2 mg, 4 mg (Bristol-Myers Squibb K.K.) [2] Limethason Intravenous Injection 2.5 mg (Mitsubishi Tanabe Pharma Corporation) [3] Orgadrone Injection 1.9 mg, 3.8 mg, 19 mg (Sandoz Pharma K.K.) [3] Decadron Phosphate Injection 1.65 mg, 3.3 mg, and 6.6 mg (Sandoz Pharma K.K.), and the others •Prednisolone preparations [1] Predonine Tablets 5 mg (Shionogi Pharma Co., Ltd.), and the others [2] Predonine for Injection 10 mg, 20 mg, 50 mg (Shionogi Pharma Co., Ltd.) [3] Predonema Enema 20 mg (Kyorin Pharmaceutical Co., Ltd.) •Methylprednisolone preparations [1] Medrol Tablets 2 mg, 4 mg (Pfizer Japan Inc.) [2] Solu-Medrol for Intravenous Use 40 mg, 125 mg, 500 mg, 1000 mg (Pfizer Japan Inc.) [3] Depo-Medrol Sterile Aqueous Suspension 20 mg, 40 mg (Pfizer Japan Inc.) •Cortisone/hydrocortisone preparations [1] Cortone Tablets 25 mg (Nichi-Iko Pharmaceutical Co., Ltd.) [2] Cortril Tablets 10 mg (Pfizer Japan Inc.) [3] Solu-Cortef Injection 100 mg (Pfizer Japan Inc.), and the Others [4] Solu-Cortef for Intravenous Use 250 mg, 500 mg, 1000 mg (Pfizer Japan Inc.), and the others [5] Hydrocortone Injection 100 mg, 500 mg (Nichi-Iko Pharmaceutical Co., Ltd.), and the others

Therapeutic category	Adrenal hormone preparations
Indications	Descriptions are omitted because there are many relevant drug products.

PRECAUTIONS (Revised language is underlined.)

•Dexamethasone (oral dosage form) (preparations indicated for multiple myeloma)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Tumour lysis syndrome If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

•Dexamethasone palmitate

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	It has been reported that tumour lysis syndrome occurred when dexamethasone preparations (oral dosage form and injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possibility of tumour lysis syndrome.

•Dexamethasone (oral dosage form) (preparations indicated for lymphoid tumours (excluding preparations indicated only for multiple myeloma))
•Dexamethasone sodium phosphate (injections)
•Prednisolone (oral dosage form)
•Prednisolone sodium succinate
•Methylprednisolone
•Methylprednisolone sodium succinate
•Methylprednisolone acetate
•Hydrocortisone
•Hydrocortisone sodium succinate (preparations indicated for lymphoid tumours)

[Under old instructions]

Important Precautions (newly added)	Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
Adverse Reactions **Clinically Significant Adverse Reactions (newly added)**	Tumour lysis syndrome: Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	<Common to all indications> Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc. Tumour lysis syndrome

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

•Prednisolone sodium phosphate

[Under new instructions]	
8. IMPORTANT PRECAUTIONS **(newly added)**	It has been reported that tumour lysis syndrome occurred when prednisolone preparations (oral dosage form and injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possibility of tumour lysis syndrome.

•Cortisone acetate

[Under new instructions]	
8. IMPORTANT PRECAUTIONS **(newly added)**	It has been reported that tumour lysis syndrome occurred when hydrocortisone preparations (injections) were administered to patients with lymphoid tumours. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Tumour lysis syndrome Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

•Hydrocortisone sodium succinate (preparations not indicated for lymphoid tumours),
•Hydrocortisone sodium phosphate

[Under old instructions]	
Important Precautions **(newly added)**	It has been reported that tumour lysis syndrome occurred when hydrocortisone preparations (injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possibility of tumour lysis syndrome.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS **(newly added)**	It has been reported that tumour lysis syndrome occurred when hydrocortisone preparations (injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) falling under MedDRA PT “tumour lysis syndrome” in which no antineoplastics were concomitantly used for the treatment of lymphoid tumours among cases collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving tumour lysis syndrome reported in Japan: Dexamethasone preparations: 1 (No patient mortalities) Prednisolone preparations: 3 (No patient mortalities) Methylprednisolone preparations: 2 (No patient mortalities) Cortisone/hydrocortisone preparations: 0 Cases involving tumour lysis syndrome reported overseas:

Dexamethasone preparations: 9 (2 patient mortalities)
Prednisolone preparations: 3 (No patient mortalities)
Methylprednisolone preparations: 7 (No patient mortalities)
Cortisone/hydrocortisone preparations: 3 (No patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Descriptions are omitted because there are many relevant drug products.
Japanese market launch: Descriptions are omitted because there are many relevant drug products.

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
Under
10 years
old</td><td>T-cell type acute
leukaemia
(none)</td><td>4 mg
for 1 day
↓
42 mg
Unknown</td><td>Tumour lysis syndrome
4 hours before administration: A blood test revealed a white blood cell count of 80×10^4/μL, and the patient was transported by ambulance with suspected acute leukemia. By the presence of large thymus gland, the patient was provisionally diagnosed with T-cell type acute leukaemia, and the treatment was started. Potassium and phosphorus levels were within the normal range, and urine output was maintained. However, there was a concern about the occurrence of tumour lysis syndrome indicated by the severe hyperuricaemia (16.8mg/dL) and abnormally high WBC levels. Therefore, in addition to hydration, rasburicase (genetical recombination) was administered.
At the start of initial administration: The blood test after 4 hours of administration of rasburicase (genetical recombination) revealed an improvement in uric acid with a value of 3.5 mg/dL. Therefore, chemotherapy was slowly initiated with 4 mg of prednisolone.
5 hours after initial administration (at the time of onset): Suddenly, ventricular tachycardia occurred (with confirmed hyperkalaemia), resulting in cardio-respiratory arrest. The response to epinephrine and cardiac massage was favorable. The blood test at the sudden change revealed hyperuricaemia (11.7mg/dL) and hyperphosphataemia (10.5mg/dL) in addition to hyperkalaemia (7.6mEq/L). Also, elevation in serum creatinine (1.14mg/dL) and decreased urine output were noted. Therefore, acute blood purification therapy was performed soon after resuscitation. At the same time, administration of 42 mg of prednisolone was initiated.
At the start of re-administration: On the next day of initiating chemotherapy, the WBC count was 5 700/μL, returning to the normal level.
24 hours after readministration: Improvement of laboratory test values and urine output were observed.
48 hours after re-administration: Withdrawing from dialysis became possible.
Approximately 2 weeks after re-administration: Although WBC count and the condition of tumour lysis syndrome improved, the patient was judged as brain-dead due to intracranial haemorrhage, and his death was confirmed.</td></tr>
</table>

Laboratory test value

	4 hours before administration	Initial administration	5 hours after initial administration (at the time of onset)	12 hours after initial administration	1 day after re-administration	2 days after re-administration
Uric acid (mg/dL)	16.8	3.5	11.7	6.6	1.6	0.2
Potassium (mEq/L)	3.7	4.2	7.6	5.1	3.3	3.5
Posphoric acid (mg/dL)	5.1	—	10.5	—	—	—
Calcium (mg/dL)	9.2	—		—	—	—
Serum creatinine (mg/dL)	0.43	—	1.14	—	—	—

Suspected concomitant drugs: None
Concomitant drugs: Rasburicase (genetical recombination)

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>2</td><td>Male
Under 10 years old</td><td>Burkitt's lymphoma stage IV
(none)</td><td>10 mg
Unknown</td><td>Tumour lysis syndrome
Approximately 6 months before administration: Abdominal tumour was pointed out.
5 days before administration: The patient was admitted to this department. At the time of admission, tumour with a size of 5×8×8cm by a CT and echo was confirmed. A bone marrow test at the time of admission showed 4% blasts.
1 day before administration: Blasts increased to 90%. The patient was diagnosed with Burkitt's lymphoma stage IV by the cell surface marker test of blasts. Transfusion (3 000 mL/m^2/day) was given, and diuretics and allopurinol were administered.
Day 1 of administration: 10 mg/day of prednisolone was intravenously administered.
1 day after administration (date of onset): Serum phosphorus markedly increased to 13.3 mg/dL. Renal function decreased. Renal failure (BUN 50 mg/dL, creatinine clearance 3 mL/minute) was considered, and peritoneal dialysis was initiated.
2 days after administration: Serum phosphorus decreased.
3 days after administration: Chemotherapy was initiated. No abnormalities were noted in serum phosphorus and calcium, and chemotherapy could be performed as previously planned.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table>
<tr><th></th><th>1 day after administration
(date of onset)</th></tr>
<tr><td>Uric acid (mg/dL)</td><td>−</td></tr>
<tr><td>Potassium (mEq/L)</td><td>−</td></tr>
<tr><td>Serum phosphorus (mg/dL)</td><td>13.3</td></tr>
<tr><td>Calcium (mg/dL)</td><td>−</td></tr>
<tr><td>BUN (mg/dL)</td><td>50</td></tr>
<tr><td>Creatinine clearance (mL/minute)</td><td>3</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Suspected concomitant drugs: None
Concomitant drugs: Allopurinol, diuretics</td></tr>
</table>

3 Atezolizumab (genetical recombination)

Brand name (name of company)	Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic category	Other antitumor agents
Indications	<Tecentriq for Intravenous Infusion 1200 mg> •Unresectable, advanced or recurrent non-small cell lung cancer •Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer •Extensive-stage small cell lung cancer •Unresectable hepatocellular carcinoma <Tecentriq for Intravenous Infusion 840 mg> •PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Encephalitis, meningitis, myelitis
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving myelitis reported in Japan: 2 (No patient mortalities) Cases involving myelitis reported overseas: 3 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 15 343 Japanese market launch: Tecentriq for Intravenous Infusion 840 mg: November 2019 Tecentriq for Intravenous Infusion 1200 mg: April 2018

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Male 70s	Hepatocellular carcinoma (hypertension, hepatic cirrhosis)	1 200 mg/dose every 3 weeks (2 courses)	**Encephalomyelitis** [PS at initiation of administration of atezolizumab] 1 [Metastases] Lymph nodes: Site (around the abdominal aorta) [Previous treatment drug] lenvatinib mesilate [History of surgery] partial hepatectomy of S6 [Other treatment history] Transcatheter arterial embolization (TAE), endoscopic injection sclerotherapy (EIS) Day 1 of administration: Administration of atezolizumab + bevacizumab was initiated. Oedema occurred. 1 day after administration: Diarrhoea (grade 3 at worst), pyrexia (grade 3 at worst), depressed level of consciousness (grade 3 at worst), and impaired appetite occurred. Therapeutic measures included *Clostridium butyricum* combination drug and loperamide hydrochloride. 15 days after administration: The patient experienced disturbed consciousness and pyrexia. Head MRI and cerebrospinal fluid test showed no abnormal findings. 16 days after administration: The patient was admitted to the hospital (for 8 days). Ceftriaxone sodium hydrate and vitamins were administered for increased CRP, and the pyrexia subsided. 26 days after administration: The patient's appetite normalized. 41 days after administration (day of completion of administration): The patient received the second dose of atezolizumab + bevacizumab. 1 day after completion: Diarrhoea, impaired appetite, and encephalomyelitis (grade 3) occurred. – : The patient had to pull himself up with a handrail to go up the stairs, and he became unable to go up the stairs any longer. 37 days after completion: With urinary retention, gait disturbance, pyrexia, diarrhoea, and impaired appetite, the patient was admitted to the hospital. The revised Hasegawa's Dementia Scale (HDS-R) was 22/30. His understanding decreased, and he repeated the same thing. Muscular weakness of the left lower extremity (level 1 on MMT below the thigh) was noted. Head MRI: Haemorrhagic infarction was positive (+) in the medial left temporal lobe (hippocampus). Small lesions with high FLAIR were scattered in the brain surface. Therapeutic measures included ceftriaxone sodium hydrate (administered for 5 days), concentrated glycerin/fructose combination drug (administered for 6 days), and steroid pulse therapy (administered for 3 days). 41 days after completion: There was no improvement in the symptoms. Muscular weakness in the left lower extremity (level 1 on MMT), decrease of temperature and pain sensation below the right chest, and neurogenic bladder were noted. The tendon reflex was normal or increased (+). 43 days after completion: A thoracic spinal cord MRI showed a T2-high intensity lesion at Th2-4 mainly on the

				left side, and the patient was diagnosed with myelitis. He received steroid pulse therapy (administered for 3 days). A cerebrospinal fluid test showed a cell count of 415/3 (mononuclear cell-dominant), protein of 112.8, anti-aquaporin-4 antibody negative (-) and oligoclonal band negative (-). 44 days after completion: The patient's cognitive function normalized with steroid pulse therapy. 45 days after completion: A head MRI showed a tendency toward shrinkage in the hyperintensity area. HDS-R was 26/30. The patient was recovering from encephalomyelitis. He had not recovered from oedema.

Laboratory test value

Test item (unit)	15 days after administration	41 days after administration (day of completion of administration)	37 days after completion	43 days after completion
White blood cells (/mm^3)	2 100	2 300	3 900	4 000
Lymphocytes (/mm^3)	390	610	410	580
Neutrophils (/mm^3)	1 510	1 380	3 300	3 010
Eosinophils (/mm^3)	10	160	0	220
Basophils (/mm^3)	30	20	10	10
Anti-neutrophil myeloperoxidase antibody (MPO-ANCA)	–	–	–	Less than 1.0 U/mL
Antinuclear antibody	–	–	–	Less than 40
CRP (mg/dL)	8.4	0.26	2.35	0.12
BUN (mg/dL)	20.6	10.1	22.2	–
Serum creatinine (mg/dL)	1.09	0.75	1.45	–
AST (GOT) (IU)	40	55	30	–
ALT (GPT) (IU)	24	40	15	–
CK (CPK) (IU/L)	35	59	136	–
Na (mEq/L)	135	140	136	–
K (mEq/L)	3.7	3.3	4.4	–
Ca (mg/dL)	8.4	8.8	9.3	–
Cl (mEq/L)	102	103	98	–

Concomitant drugs: Bevacizumab, corticosteroid

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
2	Female 50s	Lung adenocarcinoma (myelitis)	1 200 mg/dose for 1 day	**Aggravation of myelitis** [Underlying disease] Unresectable, advanced or recurrent non-small cell lung cancer (NSCLC) (histological type: Adenocarcinoma, stage at diagnosis: Stage IV) [Metastases] metastases to central nervous system, metastases to bone, metastases to lung [ECOG_PS] 2 [History of previous treatment] erlotinib hydrochloride, bevacizumab, osimertinib mesilate Day 1 of administration (day of completion of administration): Atezolizumab + bevacizumab + carboplatin + paclitaxel were administered. 7 days after completion: Decreased neutrophil count (grade 4 at worst) occurred. 12 days after completion: The patient could not move due to pyrexia of 39.9 °C and general malaise. She was transferred to the hospital by ambulance. As febrile neutropenia was suspected, she was admitted to the hospital for treatment. She had myelitis even before the initiation of administration of atezolizumab, due to which numbness of lower extremities and difficulty in moving them were noted. Aggravation of the symptoms was observed on the admission for febrile neutropenia. Aggravation of myelitis (grade 4 at worst), increased CK (grade 4 at worst), and febrile neutropenia (grade 3 at worst) occurred. Therapeutic measures included methylprednisolone sodium succinate, prednisolone sodium succinate for injection, and cefepime dihydrochloride hydrate (administered for 7 days). 14 days after completion: Anaemia (grade 2 at worst) and decreased platelets (grade 2 at worst) occurred. 15 days after completion: The patient underwent a cervical and thoracic spinal cord MRI, which revealed findings of myelitis at the C4-Th9 level. 16 days after completion: The MRI showed expanded lesion compared with the previous MRI. Considering the possibility of both aggravation of preexisting myelitis and irAE, administration of methylprednisolone sodium succinate was initiated. 19 days after completion: The patient recovered from febrile neutropenia. 21 days after completion: The patient recovered from decreased neutrophil count. 26 days after completion: The patient had not recovered from aggravation of myelitis with complete paralysis of the lower extremities remaining. 34 days after completion: The patient recovered from increased CK.

Laboratory test value

	12 days after completion
CK (IU/L)	1 196
Body temperature (°C)	39.9
CRP (mg/dL)	3.14
Neutrophil count (/mm^3)	505
PCT (ng/mL)	5.78

Concomitant drugs: Bevacizumab, carboplatin, paclitaxel

4 [1] Encorafenib
[2] Binimetinib

Brand name (name of company)	[1] Braftovi Capsules 50 mg, 75 mg (Ono Pharmaceutical Co., Ltd.) [2] Mektovi Tablets 15 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Other antitumor agents
Indications	•Unresectable malignant melanoma with *BRAF* mutation • Unresectable, advanced or recurrent colorectal cancer with *BRAF* mutation that has progressed after cancer chemotherapy

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Tumour lysis syndrome If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.
Reference information	Number of cases (for which a causal relationship between the drugs and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving tumour lysis syndrome reported in Japan: [1][2] 3 cases, including 1 case in which the drugs were administered outside the approved indications (No patient mortalities) Cases involving tumour lysis syndrome reported in overseas: [1][2] 5 (No patient mortalities) Number of patients using the drugs as estimated by the MAHs during the previous 1-year period: [1] Approximately 420 [2] Approximately 265 Japanese market launch: [1] Braftovi Capsules 50 mg: February 2019 Braftovi Capsules 75 mg: November 2020 [2] February 2019

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Female
50s</td><td>Malignant melanoma (metastases to pleura, hepatitis B virus carrier, pleural effusion)</td><td>Encorafenib (450 mg), binimetinib (90 mg)
for 2 days
↓
Discontinuation
↓
Encorafenib (200 mg), binimetinib (30 mg)
for 14 days
↓
Encorafenib (300 mg), binimetinib (60 mg)
for 8 days</td><td>Tumour lysis syndrome
Medical history: none
Day 1 of administration: Administration of encorafenib and binimetinib was initiated to treat unresectable malignant melanoma with BRAF mutation (recurrence, primary lesion: Skin (trunk(including buttok)), disease type: Superficial spreading, stage IV, M classification: Skin M1b, V600E mutation).
Day 2 of administration (day of discontinuation): Bilateral central serous chorioretinopathy was observed, and administration of encorafenib and binimetinib was discontinued.
1 day after discontinuation: The patient had a fever and nausea in the morning, and blood tests revealed hyperkalaemia, hyperuricaemia, and acute renal failure. She was diagnosed with tumour lysis syndrome. Fluid loading was performed so that the urine volume per hour exceeded 100 mL. Administration of oral febuxostat and diuretics was initiated.
3 days after discontinuation: Marked improvement in renal function and values for uric acid and potassium was noted.
5 days after administration: Tumour lysis syndrome improved and resolved.
8 days after discontinuation (day 1 of readministration): Administration of encorafenib and binimetinib was resumed.
Day 15 of readministration: The dose of encorafenib and binimetinib was changed.
3 weeks after readministration: No tumour lysis syndrome recurred.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table><tr><th></th><th>Day 1 of administration</th><th>1 day after discontinuation</th><th>3 days after discontinuation</th></tr><tr><td>Creatinine (mg/dL)</td><td>0.55</td><td>3.12</td><td>1.04</td></tr><tr><td>Uric acid (mg/dL)</td><td>4.5</td><td>12.4</td><td>3.9</td></tr><tr><td>Potassium (mmol/L)</td><td>5.0</td><td>6.1</td><td>3.2</td></tr><tr><td>Calcium (mg/dL)</td><td>8.4</td><td>7.8</td><td>−</td></tr><tr><td>Phosphorus (mg/dL)</td><td>4.3</td><td>9.8</td><td>−</td></tr></table></td></tr>
<tr><td></td><td colspan="4">Concomitant drugs: None</td></tr>
</table>

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>2</td><td>Female
40s</td><td>Malignant melanoma
(metastases to lymph nodes, to peritoneum, to liver, and to bone)</td><td>Encorafenib
(450 mg),
binimetinib
(90 mg)
for 4 days
↓
Discontinuation
↓
Encorafenib
(450 mg),
binimetinib
(90 mg)</td><td>Tumour lysis syndrome
The patient had no medical history, and she had a history of smoking.
Day 1 of administration: Administration of encorafenib and binimetinib was initiated to treat unresectable malignant melanoma with BRAF mutation (histological type: Malignant melanoma, primary lesion: Left third toe, stage classification: IV, TMN classification: T4aN3M1).
Day 4 of administration: (day of discontinuation): Hyperkalaemia and hyperuricaemia were observed, and the patient was diagnosed with tumour lysis syndrome. Fluid loading was initiated. Administration of encorafenib and binimetinib was discontinued.
4 days after discontinuation: Oral administration of febuxostat was initiated.
8 days after discontinuation (day 1 of readministration): Administration of encorafenib and binimetinib was resumed.
Day 7 of readministration: Tumour lysis syndrome resolved.</td></tr>
<tr><td colspan="5">Laboratory test value
<table>
<tr><th></th><th>1 day before administration</th><th>Day 4 of administration
(day of discontinuation)</th><th>Day 7 of readministration</th></tr>
<tr><td>Creatinine (mg/dL)</td><td>0.63</td><td>4.2</td><td>0.56</td></tr>
<tr><td>Uric acid (mg/dL)</td><td>5.4</td><td>14.3</td><td>0.5</td></tr>
<tr><td>Potassium (mmol/L)</td><td>4.4</td><td>5.0</td><td>3.9</td></tr>
<tr><td>Calcium (mg/dL)</td><td>9.1</td><td>8.1</td><td>7.9</td></tr>
<tr><td>Phosphorus (mg/dL)</td><td>−</td><td>−</td><td>2.6</td></tr>
</table></td></tr>
<tr><td colspan="5">Concomitant drugs: Bilastine, loxoprofen sodium hydrate, rebamipide, precipitated calcium carbonate/cholecalciferol/magnesium carbonate, tramadol hydrochloride/acetaminophen, hydromorphone hydrochloride</td></tr>
</table>

5 Pembrolizumab (genetical recombination)

Brand name (name of company)	Keytruda Injection 100 mg (MSD K.K.)
Therapeutic category	Other antitumor agents
Indications	•Malignant melanoma •Unresectable, advanced or recurrent non-small cell lung cancer •Relapsed or refractory classical Hodgkin lymphoma •Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy •Advanced or recurrent microsatellite instability-high (MSI-High) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) •Radically unresectable or metastatic renal cell carcinoma •Postoperative adjuvant therapy for renal cell carcinoma •Recurrent or metastatic head and neck cancer •Radically unresectable advanced or recurrent oesophageal carcinoma •Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer •PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer •Pre- and postoperative adjuvant therapy for hormone receptor-negative and HER2- negative breast cancer at high risk of recurrence •Unresectable, advanced or recurrent endometrial carcinoma that has progressed after cancer chemotherapy •Advanced or recurrent, tumour mutational burden-high (TMB-High) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) •Advanced or recurrent cervical cancer •Recurrent or refractory primary mediastinal large B-cell lymphoma

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Encephalitis, meningitis, myelitis
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving myelitis reported in Japan: 2 (No patient mortalities) Cases involving myelitis reported overseas: 10 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 48 000 Japanese market launch: February 2017

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 40s	Lung squamous cell carcinoma stage IV (metastatic brain tumour, multiple metastases, Basedow's disease)	200 mg, 1 course every 3 weeks (3 courses in total) ↓ discontinued ↓ 200 mg, 1 course every 3 weeks (7 courses in total at approximately 160 days after re-administration, number of doses unknown at 594 days after re-administration)	**Myelitis** 83 days before administration: The patient was found to have metastatic brain tumour. 55 days before administration: The patient was found to have metastases of squamous cell carcinoma, and she was diagnosed with primary lung cancer. 12 days before administration: Palliative radiotherapy was performed for pain from the buttock to thigh due to sacral metastases and bladder and rectal disorder (total dose: 40 Gy, site: Sacrum, until the 9 days after administration). Thereafter, numbness continued to expand and spread to the feet, and feelings of weakness of both legs additionally occurred. Day 1 of administration: Administration of pembrolizumab was initiated for non-small cell lung cancer (squamous cell carcinoma of lung, cT1cN0M1c, stage IVB) which was diagnosed as a result of metastatic brain tumour, and for multiple metastases. 42 days after administration (day of discontinuation): The third course of pembrolizumab was administered. 3 days after discontinuation (day of onset): Dysaesthesia in both upper extremities and below the precordial region appeared. The patient also noticed numbness of both hands and dysaesthesia (feeling cold) in the precordial region in addition to aggravation of numbness of both lower extremities and feelings of weakness which had occurred before the initiation of administration. Difficulty moving the hands newly appeared. She made an unscheduled visit to the hospital. Superficial hypoesthesia in the whole area below the lower cervical spinal cord and deep sensory ataxic movement disorder were noted. Administration of pembrolizumab was discontinued after the day of onset. 8 days after discontinuation: The patient visited the neurology department. She had very mild muscular weakness in the left fingers, increased tendon reflexes in the upper extremities, and intense subjective numbness in the distal extremities with left dominance (no hypoaesthesia). A cervical spine MRI revealed an extensive abnormal signal mainly in the center of the cervical spinal cord at the C2-3 level, and a lesion mainly in the posterior funiculus of the cervical and thoracic spinal cord with a contrast effect was observed. A thoracic spine MRI revealed a small lesion similar to that in the cervical spinal cord at the Th3-4 level. A head MRI showed only changes after resection of the metastatic tumour in the left parietal lobe, and no new lesions including contrast enhancement were observed. Cerebrospinal fluid test: Initial pressure 13 cmH_2O, final pressure 8 cmH_2O, cell count 6/μL (polynuclear cell to monocyte ratio =1:16), cerebrospinal fluid culture negative, cytology negative, *Cryptococcus neoformans* antigen negative, myelin basic

					protein negative, oligoclonal band negative, and no specific abnormalities were observed. Adenosine deaminase (cerebrospinal fluid): Less than 2.0 U/L, albumin (cerebrospinal fluid): 188 mg/L, IgA (cerebrospinal fluid): 0.5 mg/dL, IgG (cerebrospinal fluid): 9 mg/dL, IgM (cerebrospinal fluid): 1 mg/dL (less than 1), color: Colorless, opacity: Absent, glucose (cerebrospinal fluid): 56 mg/dL, total protein (cerebrospinal fluid): 35 mg/dL, LDH (cerebrospinal fluid): 13 U/L, Na (cerebrospinal fluid): 145 mmol/L, K (cerebrospinal fluid): 3.0 mmol/L, Cl (cerebrospinal fluid): 121 mmol/L. Blood test: Anti-aquaporin-4 antibody was negative (less than 1.5) negative, and anti-MOG antibody was negative. IgA (serum): 142 mg/dL, IgG (serum): 2197 mg/dL, IgM (serum): 134 mg/dL. Peripheral nerve conduction test: (Right midline, tibial-sural nerve) approximately within normal limits. As no specific abnormalities were observed in cerebrospinal fluid and blood tests, the condition was judged to be drug-induced autoimmune myelitis. She returned home temporarily at her request.
				10 days after discontinuation	The patient was admitted to the hospital for queasy and aggravation of numbness of the limbs.
				11 days after discontinuation	Intravenous drip infusion of methylprednisolone sodium succinate 500 mg once daily was administered for 3 days.
				17 days after discontinuation	Intravenous drip infusion of methylprednisolone sodium succinate 500 mg once daily was administered again for 3 days, and the symptoms gradually improved. The lesions also disappeared. There was no relapse thereafter. Administration of immunoglobulins/plasma exchange and antibiotics/antivirals was not performed.
				20 days after discontinuation	Numbness of the limbs and feelings of weakness gradually improved.
				21 days after discontinuation	Abnormal signals on a cervical spine MRI decreased in intensity and diminished in range.
				38 days after discontinuation	Myelitis was recovering.
				Approximately 65 days after discontinuation (Start date of re-administration)	Administration of pembrolizumab was resumed at the patient's request.
				594 days after re-administration	Administration of pembrolizumab was continued, and there was no recurrence of myelitis or other notable adverse reactions.
	Concomitant drugs: Pregabalin, levetiracetam, oxycodone hydrochloride hydrate, olanzapine, naldemedine tosilate, magnesium oxide, precipitated calcium carbonate/cholecalciferol/magnesium carbonate, lansoprazole, loxoprofen sodium hydrate, denosumab (genetical recombination)				
	Sources: Kenji Ohkita, Sayaka Yamamoto, Ken Maeno, Masahiro Omura, Takanari Toyoda, Shoji Kawashima, Masayuki Mizuno, Teppei Fujioka, Noriyuki Matsukawa 60 A case of myelitis caused by pembrolizumab The 153rd Tokai-Hokuriku Regional Meeting of the Japanese Society of Neurology; 40 Ai Fujii, Ken Maeno, Tomohiro Onuki, Hirono Nishiyama, Sayaka Yamamoto, Yoshitsugu Inoue, Norihisa Takeda, Kensuke Fukumitsu, Satoshi Fukuda, Yoshihiro Kanemitsu, Takehiro Uemura, Tomoko Tajiri, Hirotsugu Okubo, Yutaka Ito, Akio Niimi, Kenji Ohkita A-19 A case of myelitis caused by pembrolizumab The 134th Tokai Regional Society of the Japanese Society for Tuberculosis, the 116th Tokai Regional Society of the Japanese Respiratory Society, the 19th Chubu Branch Meeting of the Japan Society of Sarcoidosis and other Granulomatous Disorders; 24				

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
2	Male 60s	Bladder cancer (atrial fibrillation)	200 mg, 1 course every 3 weeks (total number of doses: unknown)	**Myelitis, limbic encephalitis** <Past medical history> Cardiogenic transient ischaemic attack Day 1 of administration: Administration of pembrolizumab was initiated for bladder cancer. 92 days after administration (day of completion): Administration of pembrolizumab was completed (total number of doses: Unknown). 548 days after completion (day of onset): Memory impairment (amnesia), numbness of the left lower extremity and transient weakness of the lower extremities appeared. 554 days after completion: An MRI was performed. 634 days after completion: An MRI was performed. Approximately 640 days after completion: Numbness of both thighs and feelings of weakness appeared. Subsequently, the symptoms worsened in 2 weeks. The patient used a wheelchair, and he had difficulty rising. 645 days after completion: Inarticulateness and sensation of sticking sputum were present. 652 days after completion: An MRI performed at another hospital showed a T2 hyperintensity in the bilateral medial temporal lobes and abnormal signals in the grey matter area from Th7 to lumbar enlargement. 653 days after completion: The patient was transferred to this hospital. Flaccid paralysis of both lower extremities, sensory disturbance of both lower extremities, and short-term memory impairment were present. Anti-AQP4 antibody was negative, thyroglobulin antibody was 13, and peroxidase antibody was less than 9. Findings on images: Compared with an MRI performed 554 days after the completion of administration of pembrolizumab, hypointensity on T1WI and hyperintensity on T2WI and FLAIR appeared in the right amygdala. A slight signal increase on DWI was suspected, but no decrease in diffusion was observed. A slight signal increase on FLAIR was also suspected in the left amygdala. Age-related ischaemic changes were seen in the bilateral cerebral white matter, but there was no significant change. No abnormality was observed in the cerebral vessels. A hyperintensity area was observed in the thoracic spinal cord grey matter below Th6 on T2WI. The lesion was largest in the lumbar enlargement. The lesion was not clear on the sagittal plane, but it may have existed in the same area even on an MRI performed 634 days after the completion of administration of pembrolizumab. A blood test revealed the following: CRP: 4.67, immunoglobulin IgG: 2 550, immunoglobulin IgA: 339, immunoglobulin IgM: 134, complement C3: 113, complement C4: 33, HbA1c: 5.2, corrected Ca level: 10.7, syphilis qualitative RPR: (-),

					RPR R.U.: 0.0, vitamin B12: 1 800, folic acid: 5.5,free triiodothyronine: 1.45, free thyroxine: 0.98, thyroid stimulating hormone: 0.495, TSH_IFCC: 0.540, WBC: 8.4 × 10^3/μL, anti-aquaporin 4 antibody: Less than 1.5, IGE (nonspecific): 849.0, vitamin B1: 27, ACE: 7.4, PR3-ANCA: Less than 1.0, MPO-ANCA: Less than 1.0, antinuclear antibody (fluorescence): 40, homogeneous: Undetected, speckled: 40, nucleolar: Undetected, peripheral: Undetected, discrete Sp. (centromere): Undetected. A cerebrospinal fluid test revealed the following: Cerebrospinal fluid-color: Clear and colorless, total cerebrospinal fluid cell count: 17, cerebrospinal fluid WBC: 17, monocytes: 16, polymorphonuclear cell: 1, other cells: 0, cerebrospinal fluid red blood cell count: 300, cerebrospinal fluid occult blood reaction: (2+), cerebrospinal fluid-protein: 121, cerebrospinal fluid-Cl: 118, cerebrospinal fluid-glucose, 51, cerebrospinal fluid IgG: 35, cerebrospinal fluid IgA: 3, cerebrospinal fluid IgM: 1
				Approximately 653 days after completion	Administration of aciclovir 675 mg was initiated (end date: Unknown).
				655 days after completion	Intravenous drip infusion of methylprednisolone sodium succinate 1000 mg once daily was administered for 3 days (the first steroid pulse).
				662 days after completion	Intravenous drip infusion of methylprednisolone sodium succinate 1000 mg once daily was administered for 3 days (the second steroid pulse). Findings on images showed improvement.
				663 days after completion	Hoarseness and bulbar symptoms appeared.
				667 days after completion	Decreased blood pressure, hypoventilation and respiratory failure occurred before dawn, and the patient was admitted to the ICU. Management with intubation and mechanical ventilation was initiated. The bulbar lesions expanded. Intravenous drip infusion of polyethylene glycol-treated normal human immunoglobulin (IVIg) 25 g was administered for 5 days.
				680 days after completion	Intravenous drip infusion of methylprednisolone sodium succinate 1000 mg once daily was administered for 3 days (the third steroid pulse).
				695 days after completion	After plasma exchange therapy was performed 9 times, disturbed consciousness, higher brain dysfunction, sensory disturbance of the lower extremities, and limbic encephalitis improved. Severe bulbar palsy and flaccid paraplegia remained. As various antibodies such as anti-MOG antibody were negative, the patient was diagnosed with central nervous system immune-related adverse event (irAE).
				735 days after completion	The patient's condition stabilized, and he was transferred to another hospital for rehabilitation. Thereafter, flaccid paraplegia remained unchanged, and the patient could not leave his sickbed. Pressure sore infection was present.
				778 days after completion	The patient complained of numbness of the lower extremities and pain. Relapse was

					suspected at the rehabilitation hospital, and he was transferred to this hospital. Based on an MRI, relapse was unlikely, but pressure sore infection and respiratory tract infection repeated, with a tendency of CO_2 retention. His consciousness level also decreased. Palliation was selected after discussion on the treatment policy, and he was not placed under ventilator management. Severe paraplegia, bladder and rectal disorder, and severe sensory disturbance were present as sequelae of myelitis and limbic encephalitis. 829 days after completion The patient died of respiratory failure.
	Concomitant drugs: Unknown				
	Sources: Satoki Ito, Hazuki Watanabe, Teruyasu Kato, Tatsuru Okochi, Takahito Fukuno, Takafumi Misawa, Yuka Tanimoto, Hayato Kondo, Daiyu Honda, Yoji Goto, Kazuo Mano “B-25 A case of limbic encephalitis and myelitis developing more than one year after administration of an immune checkpoint inhibitor.” The 164th Tokai-Hokuriku Regional Meeting of the Japanese Society of Neurology; 24				

4
Revision of PRECAUTIONS (No.347)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated January 10, 2024.

1 Psychotropic agents
Sertraline hydrochloride

Brand name	Jzoloft Tablets 25 mg, 50 mg, 100 mg, Jzoloft OD Tablets 25 mg, 50 mg, 100 mg (Viatris Pharmaceuticals Japan Inc.), and the others
[Under old instructions]	
Important Precautions (newly added)	Thrombocytopenia may occur. Blood tests should be performed during the period that this drug is administered.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Thrombocytopenia
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	<Common to all indications> Thrombocytopenia may occur. Blood tests should be performed during the period that this drug is administered.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Thrombocytopenia

2 Diuretics
[1] Acetazolamide
[2] Acetazolamide sodium

Brand name	[1] Diamox Powder, Diamox Tablets 250 mg (Sanwa Kagaku Kenkyusho Co., Ltd.) [2] Diamox for Injection 500 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
[Under new instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Acute respiratory distress syndrome, pulmonary oedema If rapidly progressive dyspnoea, hypoxaemia, or chest X-ray abnormalities such as diffuse infiltrative shadow in both lungs are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

3 Adrenal hormone preparations
Cortisone acetate

Brand name	Cortone Tablets 25 mg (Nichi-Iko Pharmaceutical Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	It has been reported that tumour lysis syndrome occurred when hydrocortisone preparations (injections) were administered to patients

(newly added)	with lymphoid tumours. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Tumour lysis syndrome Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

4 Adrenal hormone preparations

Dexamethasone (oral dosage form) (preparations indicated for multiple myeloma)

Brand name	LenaDex Tablets 2 mg, 4 mg (Bristol-Myers Squibb K.K.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS **(newly added)**	Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Tumour lysis syndrome If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

5 Adrenal hormone preparations

[1] Dexamethasone (oral dosage form) (preparations indicated for lymphoid tumours)
[2] Dexamethasone sodium phosphate (injections)
[3] Hydrocortisone
[4] Hydrocortisone sodium succinate (preparations indicated for lymphoid tumours)
[5] Prednisolone (oral dosage form)
[6] Prednisolone sodium succinate
[7] Methylprednisolone
[8] Methylprednisolone sodium succinate
[9] Methylprednisolone acetate

Brand name

[1] Decadron Elixir 0.01% (Nichi-Iko Pharmaceutical Co., Ltd.), and the others
Decadron Tablets 0.5 mg, 4 mg (Nichi-Iko Pharmaceutical Co., Ltd.)
LenaDex Tablets 2 mg, 4 mg (Bristol-Myers Squibb K.K.)
[2] Orgadrone Injection 1.9 mg, 3.8 mg, 19 mg, Decadron Phosphate Injection 1.65 mg, 3.3 mg, and 6.6 mg (Sandoz Pharma K.K.), and the others
[3] Cortril Tablets 10 mg (Pfizer Japan Inc.)
[4] Solu-Cortef Injection 100 mg (Pfizer Japan Inc.), and the others
[5] Predonine Tablets 5 mg (Shionogi Pharma Co., Ltd.), and the others
[6] Predonine for Injection 10 mg, 20 mg, 50 mg (Shionogi Pharma

	Co., Ltd.) [7] Medrol Tablets 2 mg, 4 mg (Pfizer Japan Inc.) [8] Solu-Medrol for Intravenous Use 40 mg, 125 mg, 500 mg, 1000 mg (Pfizer Japan Inc.) [9] Depo-Medrol Sterile Aqueous Suspension 20 mg, 40 mg (Pfizer Japan Inc.)
[Under old instructions]	
Important Precautions (newly added)	Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Tumour lysis syndrome: Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	<Common to all indications> Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Tumour lysis syndrome Tumour lysis syndrome may occur when this drug is administered to patients with lymphoid tumours. If any abnormalities are observed, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

6 Adrenal hormone preparations

Dexamethasone palmitate

Brand name	Limethason Intravenous Injection 2.5 mg (Mitsubishi Tanabe Pharma Corporation)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	It has been reported that tumour lysis syndrome occurred when dexamethasone preparations (oral dosage form and injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possibility of tumour lysis syndrome.

7 Adrenal hormone preparations

[1] Hydrocortisone sodium succinate (preparations not indicated for lymphoid tumours)
[2] Hydrocortisone sodium phosphate

Brand name	[1] Solu-Cortef for Intravenous Use 250 mg, 500 mg, 1000 mg (Pfizer Japan Inc.), and the others [2] Hydrocortone Injection 100 mg, 500 mg (Nichi-Iko Pharmaceutical Co., Ltd.), and the others
[Under old instructions]	
Important Precautions (newly added)	It has been reported that tumour lysis syndrome occurred when hydrocortisone preparations (injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney

	injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possibility of tumour lysis syndrome.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	It has been reported that tumour lysis syndrome occurred when hydrocortisone preparations (injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration

8 Adrenal hormone preparations

Prednisolone sodium phosphate

Brand name	Predonema Enema 20 mg (Kyorin Pharmaceutical Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	It has been reported that tumour lysis syndrome occurred when prednisolone preparations (oral dosage form and injections) were administered to patients with lymphoid tumours. If rapid electrolyte abnormalities, acute kidney injury, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possibility of tumour lysis syndrome.

9 Other antitumor agents

Atezolizumab (genetical recombination)

Brand name	Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions	Encephalitis, meningitis, myelitis

10 Other antitumor agents

[1] Encorafenib
[2] Binimetinib

Brand name	[1] Braftovi Capsules 50 mg, 75 mg (Ono Pharmaceutical Co., Ltd.) [2] Mektovi Tablets 15 mg (Ono Pharmaceutical Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels, renal function, etc.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Tumour lysis syndrome If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (e.g., administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

11 Other antitumor agents

Pembrolizumab (genetical recombination)

Brand name	Keytruda Injection 100 mg (MSD K.K.)
[Under new instructions]	

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Encephalitis, meningitis, myelitis

12 Ciltacabtagene autoleucel

Brand name	Carvykti Suspension for Intravenous Infusion (Janssen Pharmaceutical K.K.)
Important Precautions (newly added)	Occurrence of lymphoid neoplasm of CAR-positive T-cell origin has been reported in patients treated with ciltacabtagene autoleucel. Although the causal relationship with ciltacabtagene autoleucel is not clear, caution should be exercised for the onset of lymphoid neoplasms.

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 adverse drug reactions (ADRs) 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 December 31, 2023)
◎: Products for which EPPV was initiated after November 1, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Bimekizumab (genetical recombination) [*1] Bimzelx Syringe for S.C. injection 160 mg, Bimzelx Autoinjector for S.C. injection 160 mg	UCB Japan Co. Ltd.	December 22, 2023
◎	Eltrombopag olamine Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	December 22, 2023
◎	Brexpiprazole [*2] Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	December 22, 2023
◎	Cefiderocol tosilate sulfate hydrate Fetroja for Intravenous Drip Infusion 1 g	Shionogi & Co., Ltd.	December 20, 2023
◎	Lecanemab (genetical recombination) Leqembi for Intravenous Infusion 200 mg, 500 mg	Eisai Co., Ltd.	December 20, 2023
◎	Difelikefalin acetate Korsuva IV Injection Syringe for Dialysis 17.5 μg, 25.0 μg, 35.0 μg	Maruishi Pharmaceutical Co., Ltd.	December 13, 2023
◎	Coronavirus (SARS-CoV-2) RNA vaccine [*3] Daichirona for Intramuscular Injection	Daiichi Sankyo Co., Ltd.	December 1, 2023
◎	Rozanolixizumab (genetical recombination) Rystiggo for S.C. Injection 280 mg	UCB Japan Co. Ltd.	November 28, 2023
◎	Rivaroxaban [*4] [1] Xarelto tablets 10 mg, [2] Xarelto fine granules 10 mg, [3] Xarelto OD tablets 10 mg, [4] Xarelto dry syrup for pediatric 51.7 mg, [5] Xarelto dry syrup for pediatric 103.4 mg, [6] Xarelto tablets 2.5 mg	Bayer Yakuhin, Ltd.	November 24, 2023
◎	Epcoritamab (genetical recombination) Epkinly Subcutaneous Injection 4 mg, 48 mg	Genmab K.K.	November 22, 2023
◎	Efanesoctocog alfa (genetical recombination) Altuviiio Intravenous 250, 500, 1000, 2000,	Sanofi K.K.	November 22, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	3000, 4000		
◎	Inclisiran sodium Leqvio for s.c. injection syringe 300 mg	Novartis Pharma K.K.	November 22, 2023
◎	Pertuzumab (genetical recombination)/ trastuzumab (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Phesgo Combination for Subcutaneous Injection MA, Phesgo Combination for Subcutaneous Injection IN	Chugai Pharmaceutical Co., Ltd.	November 22, 2023
◎	Coronavirus (SARS-CoV-2) RNA vaccine Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	November 1, 2023
	Pegaspargase Oncaspar I.V. Infusion 3750	Nihon Servier Co. Ltd.	October 2, 2023
	Ritlecitinib tosilate Litfulo Capsules 50 mg	Pfizer Japan Inc.	September 27, 2023
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	September 26, 2023
	Tralokinumab (genetical recombination) Adtralza S.C. Injection 150 mg Syringe	LEO Pharma K.K.	September 26, 2023
	Dupilumab (genetical recombination) [1] Dupixent S.C. Injection 200 mg Syringe, [2] Dupixent S.C. Injection 300 mg Syringe, [3] Dupixent S.C. Injection 300 mg Pen	Sanofi K.K.	September 25, 2023
	Lenacapavir sodium Sunlenca Subcutaneous Injection 463.5 mg, Sunlenca Tablets 300 mg	Gilead Sciences K.K.	September 13, 2023
	Futibatinib Lytgobi tablets 4 mg	TAIHO Pharmaceutical Co., Ltd.	September 7, 2023
	Pegcetacoplan Empaveli for Subcutaneous Injection 1080 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	September 4, 2023
	Eculizumab (genetical recombination) Soliris for Intravenous Infusion 300 mg	Alexion Pharma Godo Kaisha	August 23, 2023
	Ruxolitinib phosphate[*5] Jakavi Tablets 5 mg, 10 mg	Novartis Pharma K.K.	August 23, 2023
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	August 2, 2023
	Purified pineapple stem juice NexoBrid gel 5 g	Kaken Pharmaceutical Co., Ltd.	August 1, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Foslevodopa/foscarbidopa hydrate Vyalev combination subcutaneous infusion	AbbVie GK	July 26, 2023
	Anti-human thymocyte immunoglobulin, equine Atgam Intravenous Infusion 250 mg	Pfizer Japan Inc.	July 24, 2023

*1 Psoriatic arthritis (PsA), ankylosing spondylitis (AS), and non-radiographic axial spondyloarthritis (nr-axSpA) in patients who have not sufficiently responded to conventional therapies

*2 Depression/depressed state (for use only in patients who have not sufficiently responded to conventional antidepressant therapies)

*3 Prevention of infectious disease caused by SARS-CoV-2

*4 Prevention of thrombus/embolization formation in patients who have undergone the Fontan procedure

*5 Graft-versus-host disease after haematopoietic stem cell transplant (when steroids are not sufficiently effective)