Pharmaceuticals and Medical Devices Safety Information

No. 402 July 2023

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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 (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 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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This English version of PMDSI is intended to be a reference material to provide convenience for users. In

the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 402 July 2023

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**The Manuals for Management of Individual Serious Adverse Drug Reactions**		The Ministry of Health, Labour and Welfare (MHLW) prepared the Manuals for Management of Individual Serious Adverse Drug Reactions from fiscal year (FY) 2005 to 2010 and started to revise the manuals in FY 2016 based on the latest knowledge. In this issue, the progress of the revisions of manuals, further plans, and measures to increase awareness will be introduced.	5
2	**Reports from Healthcare Professionals on Adverse Drug Reactions/Infections/ Malfunctions and Post-vaccination Suspected Adverse Reactions Are to Be Sent to the PMDA Online [Report Reception Site]**		The PMDA receives reports on adverse drug reactions, infections, malfunctions, and post-vaccination suspected adverse reactions from healthcare professionals as part of safety measure operations. These reports can be efficiently submitted online via the PMDA's electronic reporting system (hereinafter referred to as "Report Reception Site"), which enables operations from preparation to submission to the PMDA of reports on adverse drug reactions, malfunctions, infections, and post-vaccination suspected adverse reactions. This article introduces its characteristics and usage, as well as the video to publicize and disseminate the Report Reception Site.	9
3	**Important Safety Information**	*P* *C*	[1] Nivolumab (genetical recombination) [2] Ipilimumab (genetical recombination) Regarding the revision of the PRECAUTIONS of drugs in accordance with the Notification dated June 13, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.	14
4	**Revision of PRECAUTIONS (No. 342)**	*P*	Haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate) (and 2 others)	18
5	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of May 31, 2023	19

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

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

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

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

ADR	Adverse Drug Reaction
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency

1
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 Ministry of Health, Labour and Welfare (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 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 2021, 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 15, 2022 and were published in April 2023.

Author	Manual title	Category: New (newly prepared) or Revision
Japanese Dermatological Association	Medicament contact dermatitis	Revision
Japanese Society of Oral and Maxillofacial Surgeons	Stomatitis medicamentosa	Revision
	Chemotherapy-induced oral mucositis (stomatitis)	Revision
Japanese Ophthalmological Society	Retinal and optic pathway disorders	Revision
Japanese Society of	Progressive multifocal	New

Neurology	leukoencephalopathy (PML)	

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 2022, the following Manuals were revised or newly drafted 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.

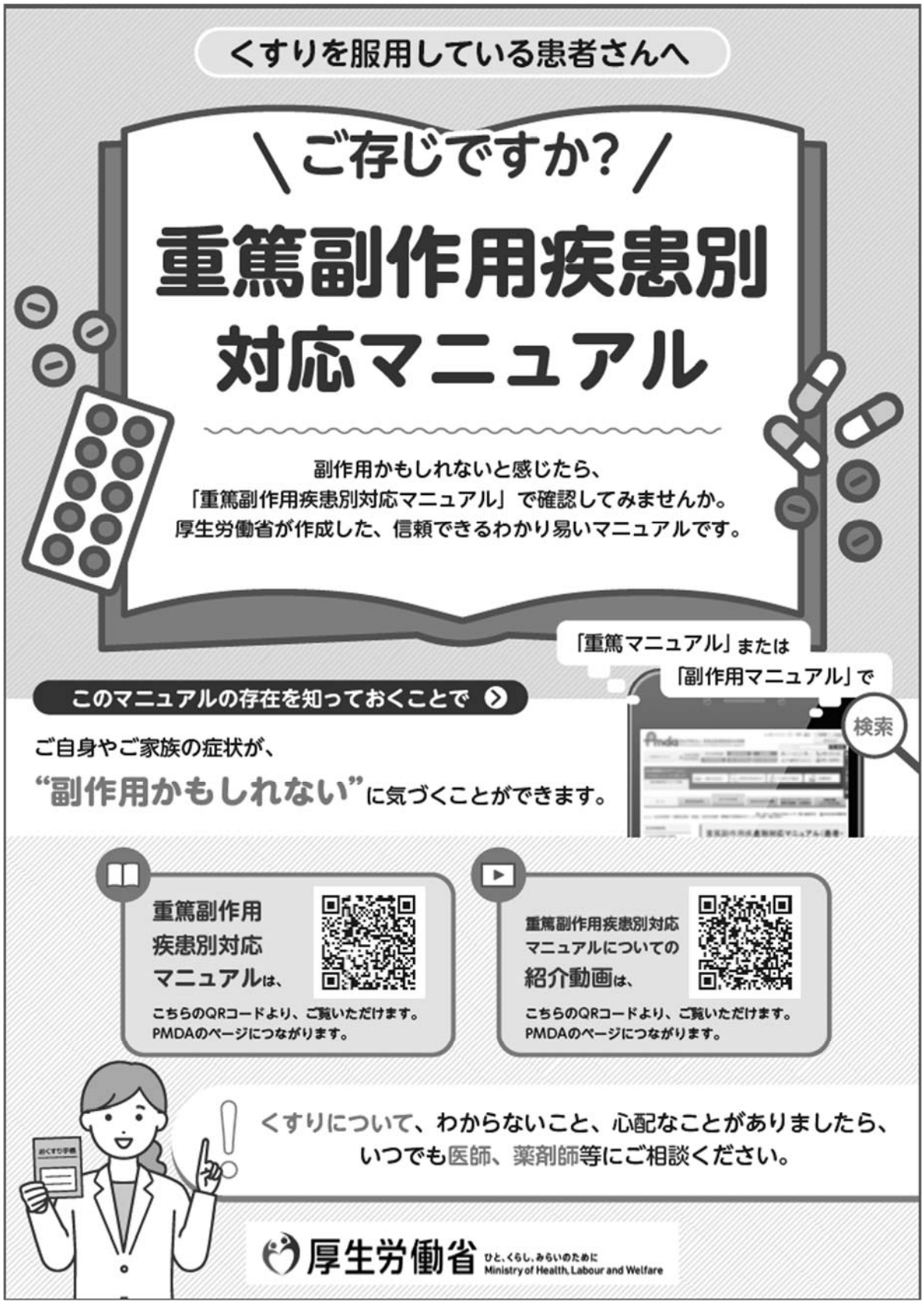
Author	Manual title	Category: New (newly prepared) or Revision
The Japanese Circulation Society	Severe hypertension	New
The Japan Diabetes Society	Hyperglycemia	Revision
	Hypoglycemia	Revision

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 March 2023, we prepared a poster introducing the manuals to patients. 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-public/0003.html) (only in Japanese).

An educational video about the Manuals prepared and published in 2022 is also available via the link above. You are encouraged to watch the video.


くすりを服用している患者さんへ
ご存じですか?
重篤副作用疾患別
対応マニュアル
副作用かもしれないと感じたら、
「重篤副作用疾患別対応マニュアル」で確認してみませんか。
厚生労働省が作成した、信頼できるわかり易いマニュアルです。
「重篤マニュアル」または
「副作用マニュアル」で
検索
このマニュアルの存在を知っておくことで
ご自身やご家族の症状が、
“副作用かもしれない”に気づくことができます。
重篤副作用
疾患別対応
マニュアルは、
こちらのQRコードより、ご覧いただけます。
PMDAのページにつながります。
重篤副作用疾患別対応
マニュアルについての
紹介動画は、
こちらのQRコードより、ご覧いただけます。
PMDAのページにつながります。
くすりについて、わからないこと、心配なことがありましたら、
いつでも医師、薬剤師等にご相談ください。
厚生労働省
ひと、くらし、みらいのために
Ministry of Health, Labour and Welfare

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)

2
Reports from Healthcare Professionals on Adverse Drug Reactions/Infections/ Malfunctions and Post-vaccination Suspected Adverse Reactions Are to Be Sent to the PMDA Online [Report Reception Site]

1. Introduction

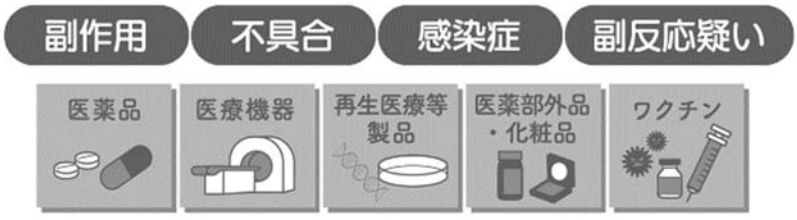
The PMDA receives reports on adverse drug reactions, infections, malfunctions, and post-vaccination suspected adverse reactions from healthcare professionals as part of safety measure operations. The information reported is used for various safety measures such as issuance of Dear Healthcare Professional Letters of Emergent Safety Communications and revision of PRECAUTIONS in the package inserts.

These reports can be submitted online via the PMDA's electronic reporting system (hereinafter referred to as "Report Reception Site"). This article introduces its characteristics, usage, etc.

2. Characteristics of the Report Reception Site

The Report Reception Site enables operations from preparation to submission to the PMDA of reports on adverse drug reactions, malfunctions, infections, and post-vaccination suspected adverse reactions to be completed efficiently online, as well as the temporary saving of reports under preparation. Electronic reports through the Report Reception Site are less susceptible to risk of wrong transmission compared with reports by FAX, etc. and cyber security is also taken into account in the site. Therefore, it can be used reliably.

<Adverse drug reactions, etc. subject to reporting>



< Major features >

· The report under preparation can be temporarily saved and reloaded.
· As input support functions, some of the data can be input using a selection-type menu or a pull-down menu.
· Files such as laboratory test values (CSV format) can be loaded.
· For reports on post-vaccination suspected adverse reactions for which attaching a questionnaire is required, the questionnaire can also be input.
· A notification will be sent via e-mail upon completion of submission or receipt of reports.

· Follow-up or similar case reports can be prepared using the Copy/Edit function of reports.
· A prepared report (including a report under preparation) can be output in PDF.

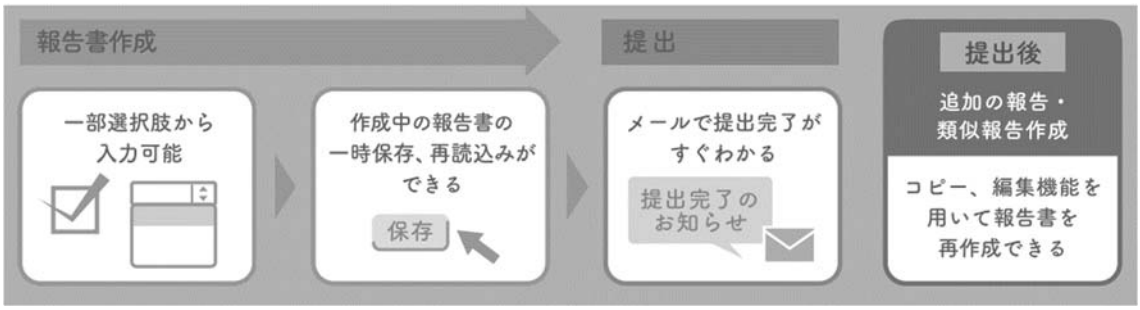
3. How to Use the Report Reception Site

The Report Reception Site can be accessed from the QR code on the right or the following PMDA website*1.

*1 The Report Reception Site on the PMDA website
https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)

<Report Reception Site>

The flow of use is as follows.

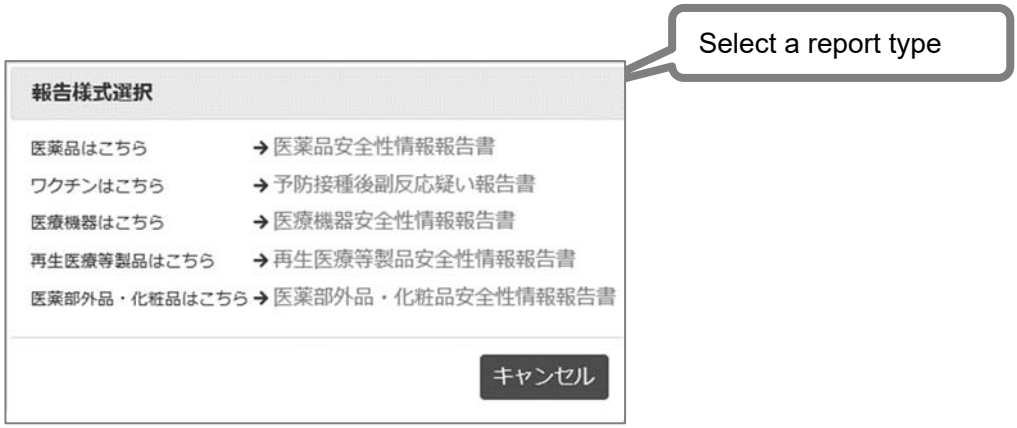


< (1) New registration/login >

If you are using the site for the first time, you need to register your user information such as your e-mail address in advance. During registration, please remember to set up and manage the secret questions required for a password reset. After registration is completed on the user information registration screen, a temporary password will be sent by e-mail. Please complete your definitive registration within 30 minutes from the temporary password being issued. After completion of the definitive registration, please log in and use it as needed.

< (2) Report list screen >

After logging in, press the "New" button on the report list screen, and then the report form selection screen will be displayed. Select the report type to be created.



< (3) Report entry >

Information on the reporter, adverse drug reaction, etc. is entered on each screen. The report under preparation can be temporarily saved and reloaded.

< (4) Submission of report >

After all the report information is entered and submitted, a notification e-mail will be sent to the registered e-mail address.

< Points to note when using the Report Reception Site >

· The Report Reception Site is a different system from the PMDA Medi-navi (No registration certificate is issued). A new registration for use is required when using the Report Reception Site.
· Your ID (your registered e-mail address), password, and secret questions and answers are the information you need to log in or reset your password. Please manage them appropriately.

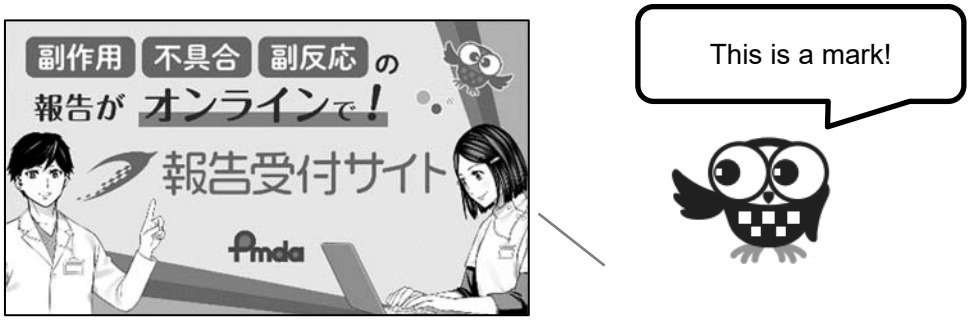
4. Conclusion

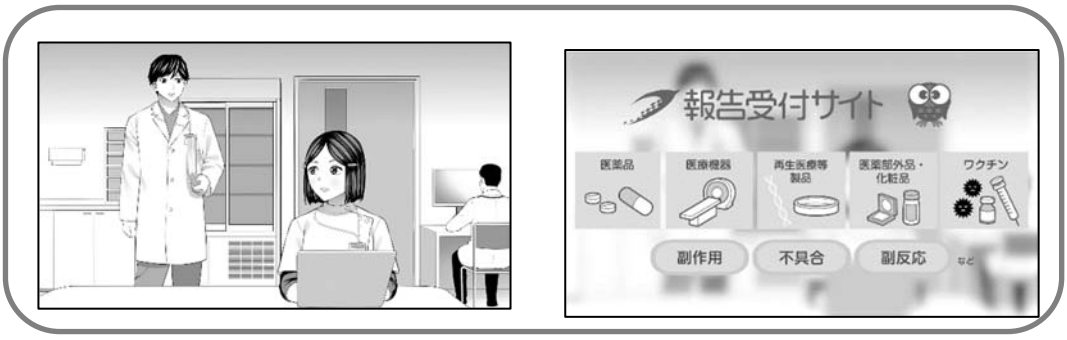
The Report Reception Site described here is also introduced in the Administrative Notice of the Ministry of Health, Labour and Welfare dated May 16, 2023 "Request for Reporting of Adverse Drug Reactions, Etc. From Healthcare Professionals Using the PMDA's Electronic Reporting System (Report Reception Site)" (https://www.pmda.go.jp/files/000252502.pdf) (only in Japanese) along with PR materials (videos and leaflets). The PR materials are also available on the Report Reception Site[*1] of the PMDA website introduced in Section 3 of this article, and they can be downloaded and used. The video is a comic format for 15 seconds or 90 seconds that provides an easy-to-understand overview of the Report Reception Site. We would appreciate it if you could cooperate in publicizing the Report Reception Site by using it during the intermission of conferences or workshops.

Reports from healthcare professionals are the source for future medical care. The active use of the Report Reception Site is encouraged, and your cooperation in reporting adverse drug reactions, etc. would be appreciated.

< Videos >

· 15-second video: Overview of the Report Reception Site and introduction of contents that can be reported
· 90-second video: In addition to the above, introduction of scenes in which the Report Reception Site is utilized and information on useful functions





You can also watch this video on PMDA's YouTube channel "Pmda Channel[*2]."

[*2] PMDA's YouTube Channel: "Pmda Channel"
https://www.youtube.com/channel/UCi7YE0LvxBQ2WYNkXNZf5Tg (only in Japanese)

< Leaflet >
Specification: A4 size, double-sided color printing

(Cover) (Back)

[Reference]

○ Pharmaceuticals and Medical Devices Safety Information Report

It is a system for healthcare professionals to report information to the Minister of Health, Labour and Welfare pursuant to the Article 68-10 Paragraph 2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) (hereinafter referred to as the "Pharmaceuticals and Medical Devices Act"). Reported information is analyzed and evaluated from a professional perspective, and then necessary safety measures are taken. In addition, the information is provided to healthcare professionals widely and utilized to ensure post-marketing safety measures for drugs, medical devices, and regenerative medical products. Reporting of quasi-drugs and cosmetics is voluntary.

· About Reporting System under Pharmaceuticals and Medical Devices Act
https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html (only in Japanese)

○ Reports on Post-vaccination Suspected Adverse Reactions

It is a system for physicians, etc. to report to the MHLW when they become aware of certain symptoms present in vaccinees pursuant to the Article 12, Paragraph 1 of the Immunization Act (Act No. 68 of 1948). Safety of vaccines is managed and reviewed based on collected information, and the information is provided to the general public widely and utilized to promote immunization administration.

· About Reporting System under Immunization Act
https://www.pmda.go.jp/safety/reports/hcp/prev-vacc-act/0003.html (only in Japanese)

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated June 13, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 [1] Nivolumab (genetical recombination)
[2] Ipilimumab (genetical recombination)

Brand name (name of company)	[1] Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.) [2] Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
Therapeutic category	Other antitumor agents
Indications	[1] •Malignant melanoma •Unresectable, advanced or recurrent non-small cell lung cancer •Neoadjuvant therapy for non-small cell lung cancer •Radically unresectable or metastatic renal cell carcinoma •Relapsed or refractory classical Hodgkin lymphoma •Recurrent or metastatic head and neck cancer •Unresectable, advanced or recurrent gastric cancer •Unresectable, advanced or recurrent malignant pleural mesothelioma •Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after chemotherapy •Radically unresectable, advanced or recurrent esophageal cancer •Postoperative adjuvant therapy for esophageal cancer •Carcinoma of unknown primary •Postoperative adjuvant therapy for urothelial carcinoma [2] •Radically unresectable malignant melanoma •Radically unresectable or metastatic renal cell carcinoma •Unresectable, advanced or recurrent microsatellite instability high (MSI-High) colorectal cancer that has progressed after chemotherapy •Unresectable, advanced or recurrent non-small cell lung cancer •Unresectable, advanced or recurrent malignant pleural mesothelioma •Radically unresectable advanced or recurrent esophageal cancer

PRECAUTIONS (Revised language is underlined.)

[1]

[Under new instructions]

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

[2]
[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	<u>Meningitis</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 Cases involving meningitis: [1] 21 (No patient mortalities) [2] 16 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 28 900 [2] Approximately 13 514 Japanese market launch: [1] Opdivo I.V. Infusion 20 mg, 100 mg: September 2014 Opdivo I.V. Infusion 240 mg: November 2018 Opdivo I.V. Infusion 120 mg: November 2020 [2] Yervoy Injection 50 mg: August 2015 Yervoy Injection 20 mg: November 2021

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
administration
duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
30s</td><td>Malignant melanoma
(metastases to lymph nodes, bone metastases)</td><td>240 mg
2-week intervals
(4 courses)
↓
80 mg
1 course</td><td colspan="2">Aseptic meningitis
The patient had a history of drinking and smoking.
Day 1 of administration: Nivolumab (240 mg) was administered for the treatment of radically unresectable malignant melanoma.
60 days after administration: Although nivolumab was administered 4 times, multiple metastases and a tendency toward recurrence were noted. Therefore, nivolumab (80 mg) and ipilimumab (300 mg) were administered as the combination therapy for radically unresectable malignant melanoma (Primary lesion: Right sole, histological type: Nodular type, stage 4, TNM classification: T4N3bM1).
72 days after administration: The patient had chills and pyrexia (in the 37°C range).
73 days after administration: The patient visited the emergency outpatient department for headache, pyrexia, and queasy.
74 days after administration (day of discontinuation): The patient visited the dermatology department. He was hospitalized to undergo a detailed examination, and the department of neurology was consulted with.
[Cerebrospinal fluid tests] Mononuclear-predominant cell count increased.
[Spinal fluid cytology] Negative
[Bacteria/virus tests] Negative
No idioblast was confirmed. Initially, viral meningitis was suspected, and acyclovir was administered by drip infusion. However, there was no improvement. Meningitis caused by nivolumab and ipilimumab was suspected. Administration of nivolumab and ipilimumab was discontinued.
5 days after discontinuation: Steroid pulse therapy (methylprednisolone sodium succinate, 1g/day) for treatment was initiated.
7 days after discontinuation: The steroid pulse therapy was highly effective. Subsequently, the dose of prednisolone was tapered.
14 days after discontinuation: The patient was discharged from the hospital.
25 days after discontinuation: Administration of prednisolone was completed after the dose was reduced to 5 mg. Aseptic meningitis resolved. Thereafter, no recurrence of symptoms was noted without resuming administration of steroid.</td></tr>
<tr><td></td><td colspan="5">Concomitant drugs: Ipilimumab</td></tr>
</table>

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
2	Female 60s	Recurrent non-small cell lung cancer (metastases to lymph nodes, constipation, insomnia)	360 mg 2 courses at 26 days intervals	**Aseptic meningitis** Hyperthyroidism, ovarian cystoma, large intestine polyp, acute hepatitis The patient had a history of drinking and smoking. Day 1 of administration: Nivolumab (360 mg), ipilimumab (47.9 mg), carboplatin (515.7 mg) and pemetrexed sodium hydrate (724 mg) were administered as the combination therapy for unresectable, advanced or recurrent non-small cell lung cancer (lung adenocarcinoma, TNM classification: T2bN3M1c, stage IVB, Oncomine Dx: KRAS Q61H, PD-L1 (22C3): 70%). 26 days after administration: The patient received the 2nd dose of nivolumab. Administration of carboplatin and pemetrexed sodium hydrate was completed. 30 days after administration: Queasy was noted. 31 days after administration: Administration of lactated Ringer's solution (with sorbitol) (500 mL/day) was initiated for treatment. 33 days after administration: The patient recovered from queasy. 46 days after administration: Pyrexia of 39 °C and headache were noted. 48 days after administration: The patient was hospitalized due to pyrexia and headache. (Day of discontinuation): [Lumbar puncture] Cell count: 29 cells/μL [Bacterial culture, HSV-PCR] Negative [Cytology] Negative for cancer cells She was diagnosed with aseptic meningitis. Prednisolone tablets (50 mg/day) was started. Administration of nivolumab and ipilimumab was discontinued. Date unknown: Headache disappeared quickly. 112 days after discontinuation: No meningitis symptoms were observed with the administration of prednisolone tablets (5 mg). Aseptic meningitis was resolving.
	Concomitant drugs: Ipilimumab, carboplatin, pemetrexed sodium hydrate, retinol/calciferol, magnesium oxide, morphine sulfate hydrate, morphine hydrochloride hydrate, lemborexant, domperidone			

4
Revision of PRECAUTIONS (No.342)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated May 29, June 13, 2023.

1 Vaccines
Haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate)

Brand name	ActHIB for S.C. Injection (Sanofi K.K.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Individuals who receive vaccinations and timing of vaccination Usually, this vaccine should be administered to individuals aged 2 months or over and under 5 years. Vaccination should be initiated at ages of 2 months or over and under 7 months as the standard practice.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Persons to be vaccinated with caution (newly added)**	Individuals with decreased immunological competence including those receiving immunosuppressive therapy (The immune response to this vaccine may be reduced. Inoculation with this vaccine should be considered with reference to the electronic package inserts of other drugs.)

2 Other antitumor agents
Ipilimumab (genetical recombination)

Brand name	Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Meningitis

3 Other antitumor agents
Nivolumab (genetical recombination)

Brand name	Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Encephalitis, meningitis

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 May 31, 2023)
◎: Products for which EPPV was initiated after April 1, 2023

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Pegvaliase (genetical recombination) Palynziq Subcutaneous Injection 2.5 mg, 10 mg, 20 mg	BioMarin Pharmaceutical Japan K.K.	May 24, 2023
◎	Mifepristone/misoprostol Mefeego Pack	Linepharma KK	May 16, 2023
◎	Treprostinil Treprost Inhalation Solution 1.74 mg	Mochida Pharmaceutical Co., Ltd.	May 16, 2023
◎	Tirzepatide Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos	Eli Lilly Japan K.K.	April 18, 2023
◎	Edaravone Radicut Ors 2.1%	Mitsubishi Tanabe Pharma Corporation	April 17, 2023
◎	Donepezil Allydone Patches 27.5 mg, 55 mg	Teikoku Seiyaku Co., Ltd.	April 14, 2023
◎	Pneumococcal 15-valent Conjugate Vaccine, Adsorbed (Conjugate with a Non Toxic Variant of Diphtheria Toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) Vaxneuvance Aqueous Suspension Syringes	MSD K.K.	April 10, 2023
◎	Isavuconazonium sulfate Cresemba Capsules 100 mg, Cresemba for i.v. infusion 200 mg	Asahi Kasei Pharma Corporation	April 6, 2023
◎	Fostamatinib sodium hydrate Tavalisse Tablets 100 mg, 150 mg	Kissei Pharmaceutical Co., Ltd.	April 6, 2023
	Cemiplimab (genetical recombination) Libtayo I.V. Infusion 350 mg	Sanofi K.K.	March 30, 2023
	Tremelimumab (genetical recombination) Imjudo Injection 25 mg, 300 mg	AstraZeneca K.K.	March 15, 2023
	Ferric derisomaltose		

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	MonoVer for I.V. Injection 500 mg, 1000 mg	Nippon Shinyaku Co., Ltd.	March 15, 2023
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)*1 Comirnaty intramuscular injection for 5 to 11 years old (Bivalent: Original/Omicron BA.4-5)	Pfizer Japan Inc.	March 3, 2023
	Dexmedetomidine hydrochloride*2 Precedex Injections Solution 200 μg [Pfizer], 200 μg/50 mL syringe [Pfizer]	Pfizer Japan Inc.	February 24, 2023
	Risankizumab (genetical recombination)*3 Skyrizi Auto dosers 360 mg	AbbVie GK	February 13, 2023
	Meningococcal polysaccharide-tetanus toxoid conjugate (serogroups A, C, W, and Y) MenQuadfi intramuscular injection	Sanofi K.K.	February 10, 2023
	Abaloparatide acetate Ostabalo Subcutaneous Injection Cart 1.5 mg	Teijin Pharma Limited.	January 30, 2023
	Risankizumab (genetical recombination) Skyrizi Intravenous infusion 600 mg	AbbVie GK	January 13, 2023
	Caplacizumab (genetical recombination) Cablivi Injection 10 mg	Sanofi K.K.	December 23, 2022
	Valemetostat tosilate Ezharmia Tablets 50 mg, 100 mg	Daiichi Sankyo Co., Ltd.	December 20, 2022
	Ozoralizumab (genetical recombination) Nanozora 30 mg Syringes for S.C. Injection	Taisho Pharmaceutical Co., Ltd.	December 1, 2022

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

*2 Sedation of non-intubated pediatric patients in non-invasive procedures and examinations

*3 Maintenance therapy for moderately to severely active Crohn's disease (only for patients who have not adequately responded to conventional treatments)