Pharmaceuticals and Medical Devices Safety Information

No.382 April 2021

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only 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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No.382 April 2021

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Labour and Welfare, 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 medical and pharmaceutical providers.

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

Abbreviations

ADR	Adverse drug reaction
CK	Creatine kinase
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
FPMAJ	Federation of Pharmaceutical Manufacturers' Associations of Japan
Fr	Fraction
FT	Free thyroxine
Gy	Gray
ITP	Idiopathic thrombocytopenic purpura
JFMDA	The Japan Federation of Medical Devices Associations
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MR	Medical Representative
NSCL	Non-small cell lung cancer
PI	Package insert
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PS	Performance status
TMA	Thrombotic microangiopathy
TSH	Thyroid stimulating hormone

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PI (Package insert)-navi, A Smartphone App Designed for Digitized Package Inserts

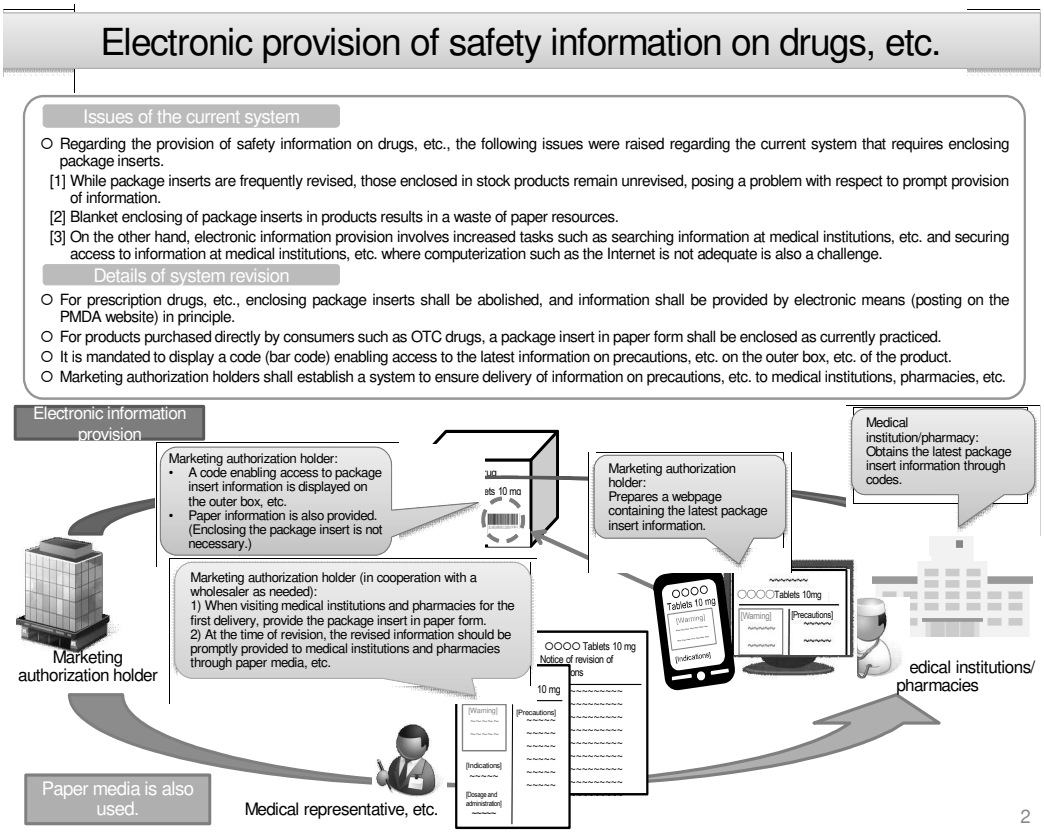
1. Introduction

Digitization of package inserts was decided as a result of the revision 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 "PMD Act") in 2019, and will begin service from August 1 of this year.

This section introduces an application for healthcare professionals (hereinafter referred to as “app”) which is a convenient tool for browsing documents published on the PMDA’s website (hereinafter referred to as “digitized package inserts”)[Note1] that describe necessary precautions, etc. for use and handling of prescription drugs, medical devices (excluding those intended to be provided primarily for the ordinary use of general consumers) and cellular and tissue-based products (hereinafter referred to as "information on precautions, etc.") [Note2] The app can be installed on mobile devices such as smartphones and tablets for convenient access to the information.

Note 1) A document containing information on precautions, etc. attached to drugs, etc., will be called a "package insert" as it was before the revision of the act. A "digitized package insert" is a document containing information on precautions, etc. published on the PMDA website.

Note 2) Although the content of the information itself is unaltered, the previous name of the information "package insert language, etc." was changed to "information on precautions, etc."



2. Browsing package inserts using an electronic method (app)

As described in 1., information on proper use and safety of drugs, etc. will be basically

accessed through digitized package inserts published on the PMDA's website in place of paper media.

The latest digitized package inserts can be searched and browsed on the PMDA's website where they are published, or the code (GS1 code) displayed on the containers, etc. of drugs, etc. can be read by the app on a smartphone or a similar electronic device for quick and convenient access to the information.

The Distribution System Research Institute (GS1 Japan), the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ), and the Japan Federation of Medical Devices Association (JFMDA) have jointly developed the app. It is called PI (Package Insert)-navi and has been available free of charge since April 1, 2021.

Introduction of PI-navi to medical and pharmaceutical professionals will start in early May. For the provision and dissemination of PI-navi, an easy-to-understand leaflet and instruction video will also be provided. Related information will be posted on the PMDA's website as part of the efforts to be made in cooperation with the industry to facilitate convenient use of PI-navi by medical professionals in clinical settings.

3. Basic operation of the app (PI-navi)

(1) Download
Download PI-navi. PI-navi can be downloaded from the official Apple or Android Stores.

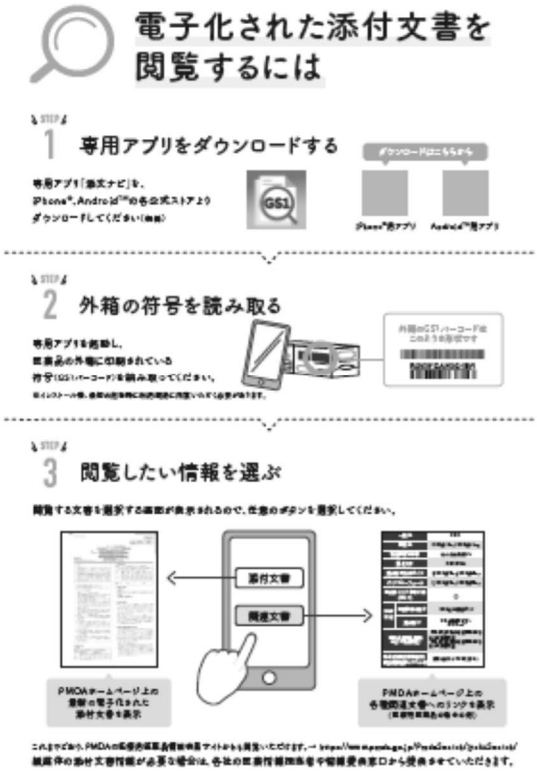
iOS

Android

(2) Read the barcode
Locate the GS1 barcode on the package of drugs, etc. Launch PI-navi and hold the device over the GS1 barcode to start the app to read the barcode. A yellow dot will appear when reading is complete and the read data are displayed.

(3) Select data of interest
When the code is read, tap the Package Inserts or Related Documents button to display the document.

Browsing digitized package inserts (only in Japanese)

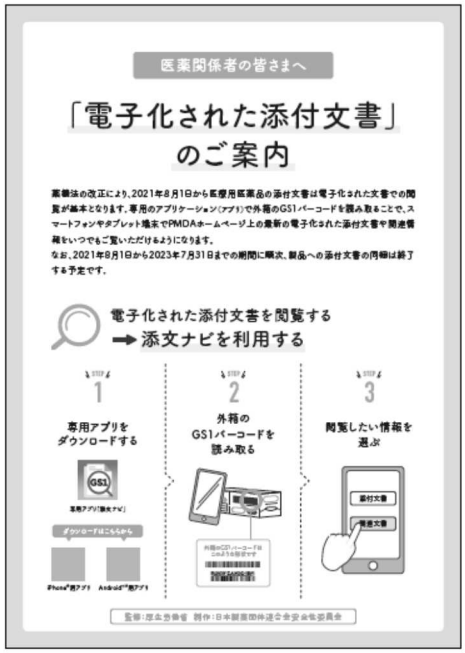


(4) Check safety information in a timely manner (PMDA Medi-navi)
Besides the PI-navi, the PMDA Medi-navi, which is a free mailing service by PMDA, is also available to subscribe for the quickest access to emergency safety information, revisions of precautions, or new drug approval.
The PMDA Medi-navi service can be subscribed to from a smartphone.
The My Drug List for Safety Update, an optional service of the PMDA Medi-navi, has released a new bulk downloading function for package inserts of prescription drugs. The bulk-downloading feature was built in line with the digitization of package inserts intended for periodic downloading of package inserts of prescription drugs by medical professionals as routine preparedness work for possible network interruption in a disaster or other accidents to ensure the availability of package inserts for reference. Medical professionals are encouraged to subscribe to the My Drug List for Safety Update as well for periodic downloading.

4. Future efforts for publicity

As mentioned earlier, introduction of PI-navi to medical professionals will start in early May. In offering and disseminating PI-navi, we will work in collaboration with the industry.

Introduction to Digitized Package Inserts: To Medical Professionals
(only in Japanese)



The medical industry plans to start publicity efforts in early May. For the publicity efforts, MRs first will explain how to download PI-navi and then encourage active use of the app. Posting videos and guidance materials on the website and distribution of printed materials including DSU (Drug Safety Update) are also intended.

Further publicity efforts are also planned to capture opportunities such as seminars, training courses, and academic conferences in cooperation with the industry and healthcare professional organizations.

5. Closing remark

Digitization of package inserts will start on August 1 of this year. This digitization of package inserts is expected to further promote the proper and safe use of drugs, etc. in medical practice.

Medical professionals in clinical practice are requested to download the PI-navi to a smartphone or other electronic devices that can be connected to the Internet by August 1 2021.

[References]

- Provision of Information on Precautions, etc. for Drugs, etc.
  https://www.mhlw.go.jp/content/000741989.pdf (only in Japanese)
- Questions and Answers (Q&A) on Provision of Information on Precautions, etc. for Drugs, etc.”
  https://www.mhlw.go.jp/content/000741990.pdf (only in Japanese)
- Points for Consideration concerning Notification, etc. of Information on Precautions, etc.
  https://www.mhlw.go.jp/content/000741991.pdf (only in Japanese)
- Digitization of Package Inserts page
  https://www.pmda.go.jp/safety/info-services/0003.html (only in Japanese)
- PMDA website PMDA Medi-navi
  https://www.pmda.go.jp/safety/info-services/medi-navi/0007.html (only in Japanese)
- My Drug List for Safety Update Service
  https://www.pmda.go.jp/safety/info-services/medi-navi/0012.html (only in Japanese)
- Digitization of Package Inserts and GS1 Standards: GS1 Japan Special Website

- https://www.dsri.jp/standard/healthcare/tenbunnavi/index.html (only in Japanese)
- Digitization of Package Inserts of Prescription Drugs: FPMAJ Special Website
- http://www.fpmaj.gr.jp/Library/eMC/index.htm (only in Japanese)
- GS1-128 Reading App Q&A Service for Medical Devices (only in Japanese)
  (intended for medical devices-related companies)
- (web delivery) Digitization of Package Inserts Briefing
  Available: March 22 to July 30 2021
  Go to the Seminar page on the JFMDA website
  https://www.jfmda.gr.jp/course/ (only in Japanese)

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Digitization of Reports from Medical Institutions on Adverse Drug Reactions and Post-vaccination Suspected Adverse Reactions

1. Introduction

Drug Safety Information Report is a system for medical professionals to report, to the Minister of Health, Labour and Welfare, information on adverse health effects, etc. (adverse drug reactions, infections) that they encounter in clinical settings as a result of drug use pursuant to the provision of Article 68-10, Paragraph 2 of the PMD Act. The system aims to analyze and evaluate reported information from a professional perspective, take necessary safety measures, provide information to medical professionals widely, and ensure post-marketing safety measures for drugs.

The Post-vaccination Suspected Adverse Reaction Report is a system for physicians, etc. to report to the MHLW when they become aware of certain symptoms present in vaccinees pursuant to the provision of Article 12-1 of the Preventive Vaccination Law. Collecting information on various physical reactions or suspected adverse reactions following vaccination, managing and reviewing safety of vaccines, the system aims to extensively inform the general public and contribute to the promotion of the current and future immunization administration.

Drug safety information is currently reported by post, FAX, or e-mail, and post-vaccination suspected adverse reactions are reported by FAX. In addition to the current modes of reporting, medical professionals will be able to electronically report to PMDA by entering information directly on the agency's website from April 1, 2021.

2. Digital report system (system name: Report Reception Site)

Medical professionals can prepare drug safety or post-vaccination suspected adverse reactions reports online at the Report Reception Site of the PMDA's website and submit the reports to the agency. Input from a PC is basically assumed but tablets can be used as well. The Report Reception Site allows the process from preparation to submission of a report to be completed in one seamless operation with no need of a paper report form. In the course of the preparation, data specific input windows will appear one by one for the reporter to follow and enter the data. For the convenience of input, a pull-down menu will list options when applicable, and reportable symptoms will appear corresponding to the name of the vaccine from which to choose in the post-vaccination suspected adverse reactions reports. When input operation is interrupted, the report under preparation can be saved. Completed reports can be stored in the system for later reuse chosen from the list of past reports to prepare a follow-up or new report. Digital reports that use the Report Reception Site are inherently free from risk of wrong transmission unlike other modes of reporting.

Users are required to agree with the terms of use and register their data including an e-mail address. Users login with their login ID (an e-mail address) and password, choose the type of report (drug safety information reports or post-vaccination suspected adverse reactions reports), and prepare a report.

Please note that a report with an attached PDF file, etc. is not accepted due to security considerations against virus contamination. For the drug safety information report, files of laboratory data, etc. (CSV format) can be read into the Report Reception Site.

< Suspected drugs input screen for drug safety information reports>

(only in Japanese)

＜医薬品安全性情報報告書 被疑薬入力画面＞

<Symptoms input screen for post-vaccination suspected adverse reactions reports>
(example for pneumococcal 23-valent vaccine, only in Japanese)

PMDA will streamline the information it receives or conduct an investigation concerning such information and notify results to the Minister of Health, Labour and Welfare. The agency will also notify the MAHs of the drugs of such information, with the name and date of birth of patients (vaccinees) generally removed. PMDA or MAHs may contact the medical institutions or other reporting entities for details.

Reported data may be released to the public as part of safety measures with names of facilities and any parts concerning patients' privacy removed.

3. Request for cooperation in reporting

Reported drug safety information and post-vaccination suspected adverse reactions are used for safety measures such as revisions of precautions. Continued cooperation from medical professionals would be very much appreciated.

[References]

· Adverse Reactions, Infections, Malfunctions Report pursuant to the Pharmaceutical and Medical Device Act (intended for healthcare professionals)
https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html (only in Japanese)

- Suspected Adverse Reactions Report pursuant to the Preventive Vaccination Pharmaceutical and Medical Device Act (intended for healthcare professionals)
  https://www.pmda.go.jp/safety/reports/hcp/prev-vacc-act/0003.html (only in Japanese)
- Report Reception Site
  https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)
  The Report Reception Site can be accessed by reading the QR code here.

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated March 30, 2021, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Ritodrine hydrochloride (injections)

Branded name (name of company)	Utemerin Injection 50 mg (Kissei Pharmaceutical Co., Ltd.), and the others
Therapeutic category	Other agents for uro-genital and anal organ
Indications	Threatened abortion/premature labour that requires emergency treatment

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Important Precautions (newly added)

Increased risks of hypoglycaemia have been reported in preterm infants born to mothers who were administered this drug. Blood sugar levels in such neonates should be properly monitored regardless of the presence of symptoms, and appropriate measures should be taken if any abnormalities are observed.
Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with magnesium sulfate hydrate (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

Drug Interactions Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Magnesium sulfate hydrate (injection)	Increased risks of hyperkalaemia have been reported in infants born preterm.	Mechanism unknown

Adverse Reactions Clinically Significant Adverse Reactions (newly added)

Neonatal hyperkalaemia: Hyperkalaemia may occur in neonates. Careful monitoring should be performed, and appropriate measures should be taken if any abnormalities are observed.

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Increased risks of hypoglycaemia have been reported in preterm infants born to mothers who were administered this drug. Blood sugar levels in such neonates should be properly monitored regardless of the presence of symptoms, and appropriate measures should be taken if any abnormalities are observed.
Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with magnesium sulfate hydrate (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates

regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

10. INTERACTIONS
10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Magnesium sulfate hydrate (injection)	Increased CK, respiratory depression, or cardiovascular adverse reactions (chest pain, myocardial ischaemia) may occur. Increased risks of hyperkalaemia have also been reported in infants born preterm.	Mechanism unknown

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Neonatal hyperkalaemia

Reference information

Number of cases (for which a causal relationship between the drug and event was reasonably possible) reported during the previous approximately 43-month period (April 2017 to October 2020)

Cases involving neonatal hyperkalaemia: 4*1 (no patient mortalities)

*1 As cases for which it could be determined that the combination of ritodrine hydrochloride and magnesium sulfate hydrate or magnesium sulfate hydrate/glucose intended for threatened premature labour or eclampsia was not administered, and that neonates (younger than 28 days old) were reported judging from their age.

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 19 000*2

*2 Number of patients using Utemerin injection

Japanese market launch: August 1986 for Utemerin Injection 50 mg

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment provided
1	Female 0 day	Maternal threatened premature labour (Maternal premature rupture of membranes)	(Transplacenta) 100 μg/min 17 days ↓ 75 μg/min 14 days ↓ 50 μg/min 12 days ↓ 30 μg/min 5 days	**Neonatal hyperkalaemia** [Maternal course] Day 1 of administration (23 weeks 6 days of pregnancy): Administration of ritodrine injection at 100 μg/min for threatened premature labour was initiated. Day 18 of administration (26 weeks 2 days of pregnancy): The dose was reduced to 75 μg/min. Day 32 of administration (28 weeks 2 days of pregnancy): The dose was reduced to 50 μg/min. Day 44 of administration (30 weeks 0 days of pregnancy): The dose was reduced to 30 μg/min. Day 48 of administration (30 weeks 4 days of pregnancy) (day of termination): Ritodrine injection was terminated. The baby was vaginally delivered shortly after the termination of administration. [Neonatal course] Female, body weight 1 574 g, height 43 cm

				Findings at birth	Apgar score: 9 points after 1 minute, 10 points after 5 minutes. Intubation and artificial respiratory management were started.
				Approx. 1 hour after birth	Infusion of glucose solution was initiated. K: 4.5 mEq/L, Na: 136 mEq/L
				Approx. 8.5 hours after birth	K: 6.8 mEq/L, Na:133 mEq/L Neonatal hyperkalaemia was noted. Furosemide was administered intravenously at 0.1 mL x 2/day.
				Approx. 16 hours after birth	K: 6.9 mEq/L, Na: 132 mEq/L Administration of dopamine at 3.8 γ was initiated for the purpose of diuresis.
				Approx. 22.5 hours after birth	Renal blood flow was confirmed to be favorable by renal echo. Diuresis was also confirmed.
				Day 1 of life	K: 4.7 mEq/L, Na: 138 mEq/L Neonatal hyperkalaemia was resolved.

Laboratory test values:

	Approx. 1 hour after birth (day of termination)	Approx. 8.5 hours after birth (at the time of onset)	Approx. 16 hours after birth (highest K value)	Day 1 of life (at the time of outcome)
K (mEq/L)	4.5	6.8	6.9	4.7
Na (mEq/L)	136	133	132	138

Concomitant drugs (mother): Ampicillin sodium, betamethasone sodium phosphate

2 Durvalumab (genetical recombination)

Branded name (name of company)	Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)
Therapeutic category	Other antitumor agents
Indications	Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy Extensive stage small cell lung cancer

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS

11.1 Clinically Significant Adverse Reactions (newly added) <u>Immune thrombocytopenic purpura</u>

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported since market launch (August 2018 to January 2021)

Cases involving immune thrombocytopenic purpura: 4 (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 400

Japanese market launch: August 2018

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reactions
	Sex/ age	Reason for use (complications)		Clinical course and treatment provided
1	Male 70s	Non-small cell lung cancer (NSCL) (chronic obstructive	540 mg 2 doses every 2 weeks	**Thrombocytopenia** Medical history: COPD, asthma, radiotherapy Others: Ex-tobacco user (15 cigarettes/day for 50 years or longer), alcohol use (Japanese wine 360 ml/day)

		pulmonary disease (COPD), hepatitis Type-B, cough)		86 days before administration	Radiotherapy was applied (radical irradiation, only to primary lesion (including metastasized lymph nodes), 63.2 Gy, 30 Fr).
				71 days before administration	Co-administration of carboplatin + paclitaxel was initiated as the primary chemotherapy (Day 1-8, or until 64 days before administration)
				56 days before administration	Carboplatin + paclitaxel were co-administered.
				49 days before administration	Carboplatin + paclitaxel were co-administered.
				42 days before administration	Carboplatin + paclitaxel were co-administered. Radiotherapy was completed.
				36 days before administration	Grade 2 leukopenia and neutropenia were observed.
				Day 1 of administration	PS: 1, Day 1 of maintenance therapy with durvalumab (540 mg/body, every 2 weeks) for NSCL (lung squamous cell carcinoma)
				Day14 of administration	The second course of maintenance therapy with durvalumab (540 mg/body) was administered.
				Day19 of administration	Chest X-ray and CT confirmed a ground glass opacity almost completely consistent with the irradiation field. Cough was noted. Considering potential microbial pneumonia, amoxicillin hydrate and potassium clavulanate 250 RS, amoxicillin hydrate 250 mg were prescribed. Sputum culture did not identify the pathogenic bacteria.
				Day 21 of administration	Assuming radiation pneumonitis/drug-induced pneumonia, oral administration of prednisolone 55 mg (1 mg/kg) was initiated. The platelet count declined to 156 000/μL.
				Day 28 of administration (day of discontinuation)	Despite the prednisolone administration, grade 4 thrombocytopenia at 4 000/μL (the lowest count declined to 1 000/μL) was noted. Emergency admission was decided. The 3rd course of maintenance therapy with durvalumab (540 mg/body) was canceled (final administration: Day 14). 20 units of platelets were transfused the same day. Minor bleeding was noted in the tongue. Rechallenge of durvalmab: None
				1 day after discontinuation	The platelet count remained at 4 000/μL. 20 units of platelets were transfused. A haematology doctor was consulted. Drug-induced thrombocytopenic purpura by durvalumab was suspected (eventually drug-induced thrombocytopenia was diagnosed with the presence of other conditions considered unlikely.) Because of its poor effectiveness, platelet transfusion was discontinued. Prednisolone was continued.
				6 days after discontinuation	Minor bleeding in the tongue improved.
				12 days after discontinuation	The platelet count was 6 000/μL. No further reduction since the previous time was noted.
				13 days after discontinuation	Bone marrow aspiration was performed, and increased megakaryocytes was noted. With no excess of blasts observed, acute leukemia was not considered likely. Prednisolone administration worked poorly. Oral administration of eltrombopag olamine 12.5 mg was initiated.

				20 days after discontinuation	The platelet count was 7 000/μL.
				26 days after discontinuation	Prednisolone was considered poorly effective and was reduced to 40mg. Eltrombopag olamine was increased to 25 mg.
				28 days after discontinuation	The platelet count was 5 000/μL. Results of bone marrow aspiration indicated no apparent bone marrow diseases. Eltrombopag olamine was increased to 37.5 mg.
				29 days after discontinuation	The patient went home to stay overnight. No issues were noted at home.
				30 days after discontinuation	The patient returned to the hospital.
				34 days after discontinuation	The platelet count was 7 000/μL.
				42 days after discontinuation	The platelet count showed a tendency to increase.
				49 days after discontinuation	The platelet count increased to 10 000/μL.
					The platelet count reached 29,000/μL. Drug-induced thrombocytopenia was considered improved.

Laboratory data

Tests (unit)	2 days before administration	Day 5 of administration	Day 14 of administration	Day 19 of administration	Day 21 of administration	Day 28 of administration
Platelet count ($\times 10^4/mm^3$)	24.5	19.5	18.1	16.6	15.6	0.4
	1 day after discontinuation	2 days after discontinuation	9 days after discontinuation	12 days after discontinuation	15 days after discontinuation	20 days after discontinuation
	0.4	0.3	0.5	0.6	0.8	0.7
	23 days after discontinuation	26 days after discontinuation	30 days after discontinuation	33 days after discontinuation	42 days after discontinuation	49 days after discontinuation
	0.7	0.5	0.7	0.9	1	2.9

Other laboratory data

Nothing noteworthy

Suspected concomitant drugs: None

Concomitant drugs: Esomeprazole magnesium hydrate, ambroxol hydrochloride, dextromethorphan hydrobromide hydrate, magnesium oxide, entecavir hydrate, acetaminophen, loxoprofen sodium hydrate, tiotropium bromide hydrate/olodaterol hydrochloride, ciclesonide, antitussive combination drugs (1), theophylline, clarithromycin, ampicillin sodium/sulbactam sodium, prednisolone, amoxicillin hydrate/potassium clavulanate, amoxicillin hydrate

Case summary 2

No.	Patient		Daily dose/ administration duration	Adverse reactions	
	Sex/ age	Reason for use/ (complications)		Clinical course and treatment provided	
2	Male 80s	Non-small cell lung cancer (benign prostatic hyperplasia, spinal osteoarthritis, hypertension, COPD, gastric ulcer, constipation, insomnia)	700 mg Every 2 weeks 6 doses	**Immune thrombocytopenia** Medical history: Radiation therapy, surgery, inguinal hernia, thrombosis Others: Ex-tobacco user (1 pack/day for 45 years), alcohol user (Japanese wine 180 ml/week)	
				41 days before administration of durvalumab (hereafter omitted)	Radiotherapy (primary lesion, chest wall and mediastina, 40 Gy, 20 Fr) was performed.
				28 days before administration	Administration of carboplatin (300 mg/dose) was initiated. Administration of paclitaxel (75 mg/dose) was initiated. (until 13 days before administration)
				21 days before administration	Paclitaxel (75 mg/dose) was administered.
				16 days before administration	Radiotherapy was completed.
				13 days before administration	Administration of paclitaxel (75 mg/dose) was discontinued.
				Day 1 of administration	PS: 0, administration of durvalumab 700 mg was initiated.
				Day14 of administration	Durvalumab 700mg was administered.
				Day 37 of administration	Durvalumab 700mg was administered.
				Day 51 of administration	Durvalumab 700mg was administered.
				Day 65 of administration	Durvalumab 700mg was administered.
				Day 86 of administration	Durvalumab 700mg was administered. The platelet count was approximately 160 000.
				Day 107 of administration	Platelet count in blood test: 10 000 (no findings were noted including bleeding)
				(day of discontinuation)	Durvalumab was discontinued (final administration: Day 86). The haematology department was consulted, and admission was decided. Bone marrow was examined, 10 units of platelets were infused, eltrombopag olamine and steroid were administered. Anticoagulant and edoxaban tosilate hydrate, which the patient was taking due to his medical history of thrombosis, were discontinued. The platelet count was 20 000, relatively low, 1 hour after transfusion.
				2 days after discontinuation	The patient's condition was considered to be grade 4 immune thrombocytopenic purpura. High dose dexamethasone (40 mg × 4 days) was administered, platelets infused, and steroid was used.
				3 days after discontinuation	Considering high TSH and low FT3, FT4 values, levothyroxine sodium hydrate 12.5 μg was initiated.
				6 days after discontinuation	High dose dexamethasone was terminated. The platelet count was 69 000.
				8 days after discontinuation	Edoxaban tosilate hydrate was resumed.
				9 days after discontinuation	Platelet count: 49 000
				13 days after discontinuation	Platelet count: 13 000 A continued tendency towards decline was indicated. Eltrombopag olamine (TPO receptor agonist) was initiated at 12.5 mg. Steroid was co-administered at the initiation. Considering a further increase in TSH, levothyroxine sodium hydrate was increased to 25 μg.
				14 days after discontinuation	Edoxaban tosilate hydrate was discontinued again.
				15 days after discontinuation	Platelet count: 15 000 No tendency towards an increase was observed.
				17 days after discontinuation	Platelet count: 15 000 No tendency towards an increase was observed.

					Considering the necessity to treat lung cancer, eltrombopag olamine was increased to 25 mg.
				20 days after discontinuation	Neither a platelet count of 10 000 nor TSH of 99.9 indicated a tendency towards improvement. Eltrombopag olamine and levothyroxine sodium hydrate were increased to 37.5 mg and 50 μg, respectively.
				22 days after discontinuation	Platelet count: 23 000 A tendency towards improvement was indicated. TSH kept on increasing.
				24 days after discontinuation	Levothyroxine sodium hydrate was increased to 100 μg.
				26 days after discontinuation	Platelet count: 56 000, TSH: 88.6
				27 days after discontinuation	Platelet count: 102 000, TSH: 66.8 Edoxaban tosilate hydrate was resumed.
				29 days after discontinuation	Platelet count: 178 000, TSH: 43.5 Both indicated a tendency towards improvement.
				30 days after discontinuation	Platelet count and thyroid functions both improved in blood tests. No particular adverse reactions in association with resumption of edoxaban tosilate hydrate were observed. The patient was discharged from the hospital.
				40 days after discontinuation	Platelet count: 162 000. The patient recovered from immune thrombocytopenia.

Laboratory data

Tests (unit)	10 days before administration	Day 1 of administration	Day 14 of administration	Day 28 of administration	Day 51 of administration	Day 65 of administration
Platelet count (x 104/mm^3)	17.0	23.7	23.4	16.0	15.1	16.5
	Day 86 of administration	Day 107 of administration 8:22	Day 107 of administration 9:07	1 days after discontinuation	6 days after discontinuation	9 days after discontinuation
	16.3	1.0	0.8	2.2	6.9	4.9
	13 days after discontinuation	15 days after discontinuation	17 days after discontinuation	20 days after discontinuation	24 days after discontinuation	26 days after discontinuation
	1.3	1.5	1.5	1	5.6	10.2
	29 days after discontinuation	40 days after discontinuation	—	—	—	—
	17.8	16.2	—	—	—	—

Other laboratory data

Nothing noteworthy

Suspected concomitant drugs: None

Concomitant drugs: Esomeprazole magnesium hydrate, clarithromycin, theophylline, amlodipine besilate, telmisartan, silodosin, magnesium oxide, lactomin, eszopiclone

Case summary 3

No.	Patient		Daily dose/ administration duration	Adverse reactions
	Sex/age	Reason for use (complications)		Clinical course and treatment provided
3	Male 40s	Non-small cell lung cancer (intervertebral disc herniation)	589 mg 1 dose	**Immune thrombocytopenia** Medical history: Intervertebral disc herniation, radiotherapy Others: Ex-tobacco user (0.5 pack/day for 17 years), ex-alcohol user (Japanese wine 3 240 ml/week) 75 days before administration of durvalumab (hereafter omitted): Radiotherapy (radical, right lung, NOS, 60 Gy, 30 Fr) was applied. 74 days before administration: The cancer was radically unresectable due to vertebral body infiltration, mediastinal infiltration, and recurrent laryngeal nerve paralysis. Chemotherapy was performed with cisplatin + tegafur/gimeracil/oteracil potassium (TS-1) regimen for 6 weeks. 34 days before administration: Radiotherapy was completed. Day 1 of administration: PS: 0, cisplatin + tegafur/gimeracil/oteracil potassium + radiotherapy was performed, followed by initiation of consolidation therapy with durvalumab. Intervertebral disc herniation was the only medical history of the patient. Thrombocytopenia was not noted at the initiation. Day 10 of administration: The platelet count was low: 7 000. Idiopathic thrombocytopenic purpura (ITP) occurred. Day 11 of administration: For the low platelet count, 20 units of concentrated human platelets were transfused. Day 15 of administration (day of discontinuation): The patient visited the hospital again. A platelet count of 6 000 indicated no improvement. Emergency admission was decided. The haematology department was consulted. Platelet-associated IgG (PA-IgG) was positive in the blood tests performed. BMA: From the ilium, both euplasia cells and all 3 types of cells were identified. No abnormalities of differentiation and maturation, and no apparent atypical cells were identified. MgK count was high and images of platelet adhesion were scarce. All of these were considered to be consistent with ITP diagnosis. The patient was treated with mPSL (methylprednisolone sodium succinate) pulse therapy 1 000 mg 1 dose/day (on Day 15 of administration) and pH4 treated human normal immunoglobulin 25 g 1 dose/day (until 4 days after discontinuation). The patient was not rechallenged with durvalumab (final administration: Day 1). 1 day after discontinuation: High dose dexamethasone (39.6 mg 1 dose/day) was initiated. 2 days after discontinuation: The platelet count improved to 29 000 in the blood test. Responses to high dose dexamethasone + immunoglobulin therapy were considered favorable. 5 days after discontinuation: Platelet count: 82 000 in the blood test. ITP was resolving. The patient could be discharged.

Laboratory data

Tests (unit)	1 day before administration	Day 10 of administration	Day 14 of administration	Day 15 of administration	2 days after discontinuation	5 days after discontinuation
Platelet count (x $10^4/mm^3$)	23.9	0.7	1.0	0.6	2.9	8.2

Other laboratory data
Nothing noteworthy

Suspected concomitant drugs: None
Concomitant drug: Lansoprazole

3 Onasemnogene abeparvovec

Branded name (name of company)	Zolgensma Intravenous Infusion (Novartis Pharma K.K.)
Therapeutic category	
Indications	Treatment of patients with spinal muscular atrophy (SMA, including those with genetically diagnosed presymptomatic SMA) who have tested negative for anti-AAV9 antibodies

PRECAUTIONS (revised language is underlined)

IMPORTANT PRECAUTIONS (newly added)	Thrombotic microangiopathy may occur. Patients should be carefully monitored for any signs or symptoms such as purpura, vomiting, or oliguria through methods including periodically performed haematology and renal function tests.
MALFUNCTION/ADVERSE REACTIONS Clinically Significant Adverse Reactions (newly added)	Thrombotic microangiopathy If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment or any other abnormalities is observed, appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event was reasonably possible) reported during the previous approximately 46-month period (April 2017 to January 2021) Cases involving thrombotic microangiopathy: 1 (no patient mortalities) Number of patients using the product as estimated by the MAH during the previous 1-year period: Approximately 30 Japanese market launch: May 2020

Case summary

Patient		Daily dose/ administration duration	Adverse reaction		Notes
Sex/ age	Reason for use (complication)		Clinical course and treatment provided		
Female	Spinal muscular atrophy (SMA) type I (none)	57.8 mL (single dose)	**Thrombotic microangiopathy (TMA)**		Spontaneous report
				The patient was diagnosed with SMA type I seven months after birth. Administration of nusinersen was initiated.
			months before administration	The final dose of nusinersen was administered.
			9 days before administration	The patient developed pyrexia of 38.2 °C 2 days prior to the scheduled administration of onasemnogene abeparvovec. CRP test was positive. Pyrexia was alleviated the next day, but administration of onasemnogene abeparvovec was postponed for 1 week.
			1 day before administration	Administration of prednisolone (1 mg/kg/day) was initiated.
			Day 1 of administration	Onasemnogene abeparvovec was administered. At the time of administration, the patient had no pyrexia.
			2 days after administration	Pyrexia of 38 °C developed. Poor appetite and decreased energy were noted.
			5 days after administration	Decreased platelet count, red blood cell schistocytes, increased LDH, increased AST, increased ALT, vomiting, diarrhoea, general physical health deterioration were noted. No significant bacteria were detected. Platelet transfusion was performed since the platelet count decreased to less than 10 000/mm^3. Prednisolone was increased to 2 mg/kg/day.

			6 days after administration	Acute kidney injury, oliguria, hypertension, decreased platelet count, and progression of anaemia were noted. Diuretics and antihypertensives were initiated. Red blood cell transfusion and platelet transfusion were performed.
			9 days after administration	Anuria was noted. The patient was diagnosed with acute renal failure based on BUN and creatinine levels. Plasma exchange was initiated (4 days). TMA was suspected due to decreased platelet count, haemolysis, and renal impairment.
			13 days after administration	Stool culture denied STEC-HUS. There was no decreased ADAMTS13 activity and TTP was ruled out. Eculizumab was administered since aHUS was also suspected.
			14 days after administration	The patient was transferred to another hospital and admitted to PICU due to overhydration, hypertension and cardiac failure caused by acute renal failure induced by TMA. Continuous hemodialysis was initiated (7 days).
			17 days after administration	Red blood cell transfusion was continued regularly for low Hb.
			21 days after administration	Continuous haemodialysis was changed to intermittent haemodialysis. It was considered that the patient should be treated as secondary TMA rather than aHUS. Therefore, the second dose of eculizumab was not administered.
			27 days after administration	Reduction of prednisolone dose was initiated.
			30 days after administration	Intermittent haemodialysis was completed.
			40 days after administration	CH50: Increased to 16.4 U/mL, The value confirmed an improvement of decreased complement by eculizumab administered 13 days after the administration of onasemnogene abeparvovec.
			49 days after administration	The patient was diagnosed with TMA (or convalescent phase of TMA) by renal biopsy conducted for definite diagnosis.
			52 days after administration	The patient was discharged from the hospital.
			61 days after administration	Microscopic haematuria, proteinuria, and urinary sugar persisted.

Laboratory test values:

Tests	2 days before admin.	5 days after admin.	6 days after admin.	7 days after admin.	9 days after admin.	19 days after admin.	26 days after admin.	40 days after admin.
Platelet count ($x10^4/mm^3$)	39.6	0.8	0.7	3.2	4.1	1.6	2.0	19.1
Hb (g/dL)	10.6	10.5	8.6	8.5	13.2	10.0	8.9	8.0
LDH (U/L)	259	2 183	2 602	3 520	4 895	1 494	665	402
AST (U/L)	24	270	251	310	422	86	45	31
ALT (U/L)	10	97	79	103	239	51	32	23
BUN (mg/dL)	11	21	36	52	37	11.7	93.7	24.9
Cre (mg/dL)	0.10	0.12	0.25	0.51	0.68	0.60	1.17	0.18
Complement C3 (mg/dL)	-	-	-	74.8	-	54.5	72.1	124.4
Complement C4 (mg/dL)	-	-	-	9.1	-	13.8	15.9	22.5
CH50 (U/mL)	-	-	-	30.7	-	<10.0	<10.0	16.4

Concomitant drugs: Prednisolone, cefotaxime sodium, omeprazole sodium, cefpodoxime proxetil, lansoprazole, famotidine

4
Revision of Precautions (No.322)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated March 30, 2021.

1 Antispasmodics
Magnesium sulfate hydrate/glucose (preparations indicated for prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy)

Branded name

Magsent Injection 100 mL, Magsent Injection Syringe 40 mL, Magnesol for Intravenous Injection 20 mL (Aska Pharmaceutical Co., Ltd.)

[Under Old instructions]

Important Precautions (newly added)

Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with ritodrine hydrochloride (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

Drug Interactions Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Ritodrine hydrochloride (injection)	Increased risks of hyperkalaemia have been reported in infants born preterm.	Mechanism unknown

2 Purgatives and clysters
Magnesium sulfate hydrate (preparations indicated for eclampsia)

Branded name

Magnesium Sulfate Hydrate "NikP" (Nichi-Iko Pharmaceutical Co., Ltd.)

[Under Old instructions]

Important Precautions (newly added)

Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered magnesium sulfate hydrate (injection) with ritodrine hydrochloride (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if mothers received this drug for eclampsia during administration of ritodrine hydrochloride (injection), and appropriate measures should be taken if any abnormalities are observed.

Drug Interactions Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Ritodrine hydrochloride (injection)	Increased risks of hyperkalaemia have been reported in infants born preterm.	Mechanism unknown

3 Other agents for uro-genital and anal organ

Ritodrine hydrochloride (oral dosage form)

Branded name

Utemerin Tablets 5 mg (Kissei Pharmaceutical Co., Ltd.), and the others

[Under Old instructions]

Adverse Reactions Clinically Significant Adverse Reactions

Occurrence of pulmonary oedema, heart failure, agranulocytosis, decreased white blood cell, thrombocytopenia, shock, arrhythmia, hepatic impairment, jaundice, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson Syndrome), pleural effusion, intestinal obstruction in mothers, heart failure in foetuses and neonates, hypertrophy of the interventricular septum wall in neonates, neonatal hypoglycaemia, and neonatal hyperkalaemia have been reported with ritodrine injections. Careful monitoring should be performed and appropriate measures should be taken if any abnormalities are observed.

[Under New instructions]

15. OTHER PRECAUTIONS
15.1 Information Based on Clinical Use

Occurrence of pulmonary oedema, heart failure, agranulocytosis, decreased white blood cell, thrombocytopenia, shock, arrhythmia, hepatic impairment, jaundice, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson Syndrome), pleural effusion, intestinal obstruction in mothers, heart failure in foetuses and neonates, reversible hypertrophy of the interventricular septum wall in neonates, neonatal hypoglycaemia, and neonatal hyperkalaemia have been reported with ritodrine injections.

4 Other agents for uro-genital and anal organ

Ritodrine hydrochloride (injections)

Branded name

Utemerin Injection 50 mg (Kissei Pharmaceutical Co., Ltd.), and the others

[Under Old instructions]

Important Precautions (newly added)

Increased risks of hypoglycaemia have been reported in preterm infants born to mothers who were administered this drug. Blood sugar levels in such neonates should be properly monitored regardless of the presence of symptoms, and appropriate measures should be taken if any abnormalities are observed. Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with magnesium sulfate hydrate (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

Drug Interactions Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Magnesium sulfate hydrate (injection)	Increased risks of hyperkalaemia have been reported in infants born preterm.	Mechanism unknown

Adverse Reactions Clinically Significant Adverse Reactions (newly added)

Neonatal hyperkalaemia: Hyperkalaemia may occur in neonates. Careful monitoring should be performed, and appropriate measures should be taken if any abnormalities are observed.

[Under New instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Increased risks of hypoglycaemia have been reported in preterm infants born to mothers who were administered this drug. Blood sugar levels in such neonates should be properly monitored regardless of the presence of symptoms, and appropriate measures should be taken if any abnormalities are observed. Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with magnesium sulfate hydrate (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

10. INTERACTIONS
10.2 Precautions for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Magnesium sulfate hydrate (injection)	Increased CK, respiratory depression, or cardiovascular adverse reactions (chest pain, myocardial ischaemia) may occur. Increased risks of hyperkalaemia have also been reported in infants born preterm.	Mechanism unknown

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Neonatal hyperkalaemia

5 Other agents for uro-genital and anal organ

Magnesium sulfate hydrate/glucose (preparations indicated for inhibition of uterine contractions in threatened premature labour, and prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy)

Branded name

Magsent Injection 100 mL, Magsent Injection Syringe 40 mL, Magnesol for Intravenous Injection 20 mL (Aska Pharmaceutical Co., Ltd.)

[Under Old instructions]

Important Precautions (newly added)

Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with ritodrine hydrochloride (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

Drug Interactions Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Ritodrine hydrochloride (injection)	Increased risks of hyperkalaemia have been reported in infants born preterm.	Mechanism unknown

[Under New instructions]

8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)

Increased risks of hyperkalaemia have been reported in preterm infants born to mothers who were co-administered this drug with ritodrine hydrochloride (injection). ECG or monitoring of serum potassium levels should be properly performed in such neonates regardless of the presence of symptoms if these drugs were co-administered to mothers, and appropriate measures should be taken if any abnormalities are observed.

10. INTERACTIONS
10.2 Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Uterine contraction inhibitors Ritodrine hydrochloride (injection)	Increased risks of hyperkalaemia have been reported in infants born preterm.	Mechanism unknown

6 Other antitumor agents

Cetuximab (genetical recombination)

Branded name Erbitux Injection 100 mg (Merck Biopharma Co., Ltd)

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Hypomagnesaemia
Hypomagnesaemia accompanied by symptoms such as prolonged QT, convulsion, numbness, or general malaise may occur. Caution should be exercised for hypocalcaemia, hypokalaemia or other electrolyte abnormalities caused by hypomagnesaemia, which may particularly exacerbate the symptoms of hypomagnesaemia. Appropriate measures should be taken such as electrolyte replacement as necessary if electrolyte abnormalities are observed.

7 Other antitumor agents

Durvalumab (genetical recombination)

Branded name Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)

[Under New instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant adverse Reactions (newly added)

Immune thrombocytopenic purpura

8 X-ray contrast agents

Iopamidol

Branded name Iopamiron Inj. 150 (50 mL), 150 (200 mL) (Bayer Yakuhin, Ltd), and the others

[Under Old instructions]

Adverse Reactions

Skin disorder: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and acute generalised exanthematous

Clinically Significant Adverse Reactions (newly added)	pustulosis may occur. Patients should be carefully monitored, and appropriate measures should be taken if symptoms such as pyrexia, erythema, small pustules, pruritus, ocular hyperaemia, or stomatitis are observed.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions <Common to all indications>**	Skin disorder Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and appropriate measures should be taken if symptoms such as pyrexia, erythema, small pustules, pruritus, ocular hyperaemia, or stomatitis are observed.

9 Cellular and tissue-based products

Onasemnogene abeparvovec

Branded name	Zolgensma Intravenous Infusion (Novartis Pharma K.K.)
IMPORTANT PRECAUTIONS (newly added)	Thrombotic microangiopathy may occur. Patients should be carefully monitored for any signs or symptoms such as purpura, vomiting, or oliguria through methods including periodically performed haematology and renal function tests.
MALFUNCTION/ADVERSE REACTIONS **Clinically Significant Adverse Reactions (newly added)**	Thrombotic microangiopathy If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment or any other abnormalities are observed, appropriate measures should be taken.

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 31 March 2021)

◎: Products for which EPPV was initiated after March 1, 2021

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Delgocitinib [1] Corectim Ointment 0.25% [2] Corectim Ointment 0.5%	Japan Tobacco Inc.	March 23, 2021
◎	Ferric citrate hydrate*1 Riona Tab. 250 mg	Japan Tobacco Inc.	March 23, 2021
◎	Lascufloxacin hydrochloride Lasvic Intravenous Drip Infusion Kit 150 mg	Kyorin Pharmaceutical Co., Ltd.	March 1, 2021
	Thalidomide*2 Thaled Capsules 25, 50, 100	Fujimoto Pharmaceutical Corporation	February 24, 2021
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection	Pfizer Japan Inc.	February 16, 2021
	Semaglutide (genetical recombination) Rybelsus tablets 3 mg, 7 mg, 14 mg	Novo Nordisk Pharma Ltd.	February 5, 2021
	Rivaroxaban*3 Xarelto tablets 15 mg, 10 mg, Xarelto fine granules 15 mg, 10 mg, Xarelto OD tablets 15 mg, 10 mg	Bayer Yakuhin Ltd.	January 22, 2021
	Cetuximab sarotalocan sodium (genetical recombination) Akalux IV Infusion 250 mg	Rakuten Medical Japan K.K.	January 1, 2021
	Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) *4 Gardasil Aqueous Suspension for Intramuscular Injection Syringes	MSD K.K.	December 25, 2020
	Baricitinib*5 Olumiant tablets 4 mg, 2 mg	Eli Lilly Japan K.K.	December 25, 2020
	Midazolam Buccolam Oromucosal Solution 2.5 mg, 5 mg, 7.5 mg, 10 mg	Takeda Pharmaceutical Company Limited.	December 10, 2020
	Enarodustat	Japan Tobacco Inc.	December 8,

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Enaroy tablets 2 mg, 4 mg		2020
Incobotulinumtoxin A Xeomin 50 units for Intramuscular injection, Xeomin 100 units for Intramuscular injection, Xeomin 200 units for Intramuscular injection	Teijin Pharma Limited.	December 4, 2020
Roxadustat*6 Evrenzo Tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 27, 2020
Dapagliflozin propylene glycolate hydrate*7 Forxiga 5 mg Tablets, Forxiga 10 mg Tablets	AstraZeneca K.K.	November 27, 2020
Cabozantinib malate*8 Cabometyx tablets 20 mg, 60 mg	Takeda Pharmaceutical Company Limited.	November 27, 2020
Binimetinib*9 Mektovi Tablets 15 mg	Ono Pharmaceutical Co., Ltd.	November 27, 2020
Encorafenib*9 Braftovi Capsules 50 mg, 75 mg	Ono Pharmaceutical Co., Ltd.	November 27, 2020
Brodalumab (genetical recombination) *10 Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Kirin Co., Ltd.	November 27, 2020
Baloxavir marboxil*11 Xofluza Tablets 20 mg, Xofluza Granules 2%	Shionogi & Co., Ltd.	November 27, 2020
Sofpironium bromide Ecclock gel 5%	Kaken Pharmaceutical Co., Ltd.	November 26, 2020
Niraparib tosilate hydrate Zejula capsules 100 mg	Takeda Pharmaceutical Company Limited.	November 20, 2020
Filgotinib maleate Jyseleca Tablets 100 mg, 200 mg	Gilead Sciences K.K.	November 18, 2020
Paliperidone palmitate*12 Xeplion TRI Aqueous Suspension for IM Injection 175 mg, 263 mg, 350 mg, 525 mg	Janssen Pharmaceutical K.K.	November 18, 2020
Oxycodone hydrochloride hydrate*13 OxyContin TR Tablets 5 mg, 10 mg, 20 mg, 40 mg	Shionogi Pharma Co., Ltd.	October 29, 2020
Glucagon Baqsimi Nasal Powder 3 mg	Eli Lilly Japan K.K.	October 2, 2020

*1 Iron deficiency anaemia

*2 Crow-Fukase (POEMS) syndrome

*3 Treatment and reduction in the risk of recurrence of venous thromboembolism

*4 Prevention of the following diseases caused by infection with human Papillomavirus (HPV) Types 6, 11, 16, and 18
・Cervical cancer (squamous cell carcinoma and adenocarcinoma) and its precancerous lesions (cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3 and cervical adenocarcinoma *in situ* (AIS))
・Vulval intraepithelial neoplasia (VIN) grades 1, 2 and 3 and vaginal intraepithelial neoplasia (VaIN) grades 1, 2 and 3
・Anal cancer (squamous cell carcinoma) and its precancerous lesions (anal intraepithelial neoplasia (AIN) grades 1, 2, and 3)
・Condyloma acuminatum
(Only underlined diseases in men are subject to EPPV)

*5 Atopic dermatitis with inadequate response to conventional treatments

*6 Nephrogenic anaemia

*7 Chronic heart failure (only in patients who are receiving standard of care)

*8 Unresectable hepatocellular carcinoma that has progressed after chemotherapy

*9 Unresectable advanced or recurrent BRAF (V-Raf murine sarcoma viral oncogene homolog B)-mutant colorectal cancer that has progressed after chemotherapy

*10 Ankylosing spondylitis and non-radiographic axial spondyloarthritis that respond inadequately to existing therapies

*11 Treatment and prevention of influenza virus infection types A and B

*12 Schizophrenia (only in patients who have been adequately treated with 4-week intramuscular paliperidone palmitate)

*13 Relief of moderate to severe chronic pain difficult to manage with non-opioid analgesics or other opioid analgesics

<Errata, 15 of page 19 in the English version of PMDSI No.381>

Original	Revised
This drug should be administered to pregnant women (those within 12 weeks before due date or in their third trimester) or women who may be pregnant only when the therapeutic benefits are considered to outweigh the risks.	This drug should be administered to pregnant women or women who may be pregnant only when the therapeutic benefits are considered to outweigh the risks.