Pharmaceuticals and Medical Devices Safety Information

No. 375 August 2020

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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 (https://www.mhlw.go.jp, only in Japanese).

Available information is listed here

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

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

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Pharmaceuticals and Medical Devices Safety Information

No. 375 August 2020

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Revisions of Precautions in Package Inserts concerning the Dosing Intervals between Different Vaccines**		Currently, package inserts of vaccines specify dosing intervals between different vaccines as 27 days or longer after live vaccines and 6 days or longer after inactivated vaccines. Based on the recent discussion at the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council, a revision of the package insert on October 1, 2020 was agreed upon to lift, while retaining the current restriction of 27 days or longer as the interval between live vaccines, the current restrictions on intervals for any other combinations of vaccines. This section will outline the revision.	4
2	**Review of Contraindications including "patients with serious renal disorder" of Parenteral Nutrition Preparations and Amino Acid Preparations for Renal Failure**	*P*	The Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council considered a revision of contraindications including "patients with serious renal disorder" of parenteral nutrition preparations and amino acid preparations for renal failure based on Japanese and overseas guidelines, statements in overseas package inserts, adverse reaction reports/studies and reports on measures taken. As a result, MHLW instructed the marketing authorization holders (MAHs) to review the Precautions in their package inserts on June 25, 2020. The details of the instruction are introduced in this section.	8
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4	**Revision of Precautions (No. 315)**	*P*	(1) Iodixanol (2) Iohexol (preparations with indications of cerebral angiography) (and 5 others)	13
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E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

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

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

Abbreviations

ADR	Adverse drug reaction
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PPN	Peripheral parenteral nutrition
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
TPN	Total parenteral nutrition

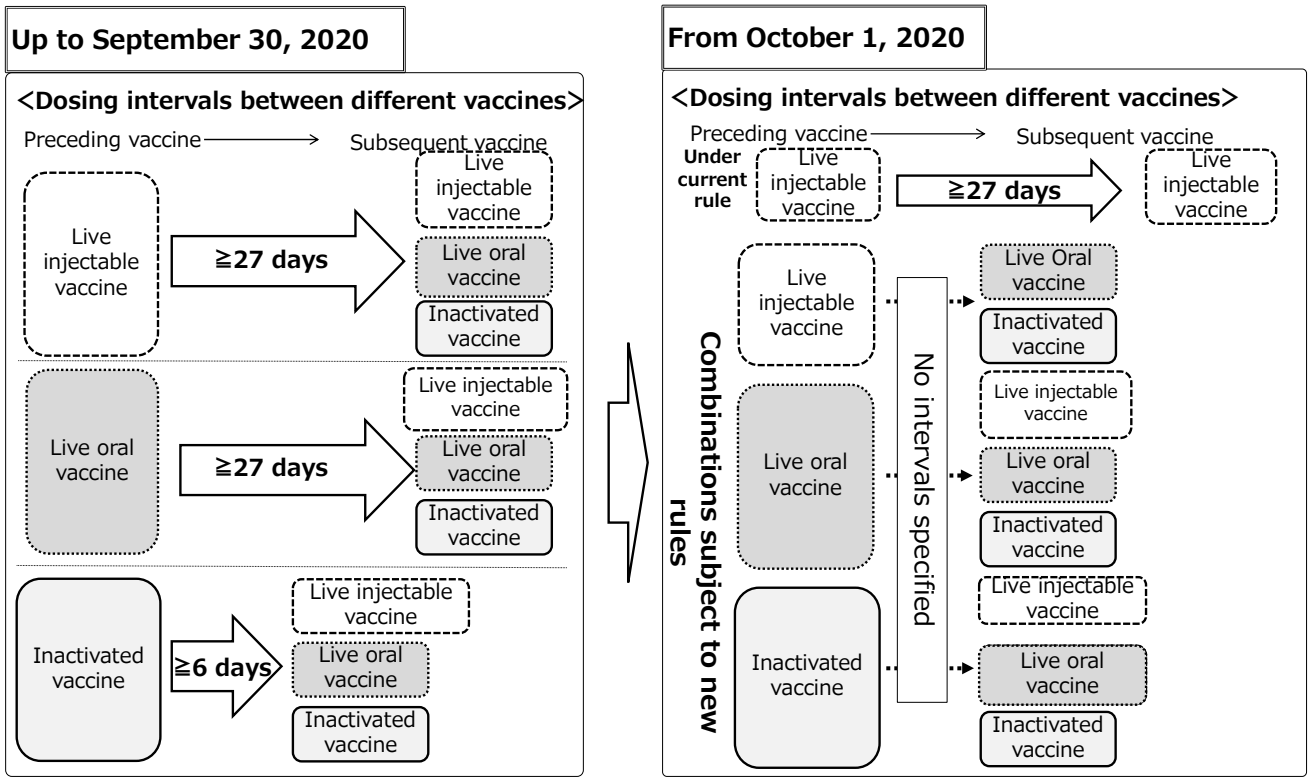
1
Revisions of Precautions in Package Inserts concerning the Dosing Intervals between Different Vaccines

1. Introduction

Currently, package inserts of vaccines specify dosing intervals between different vaccines as 27 days or longer after live vaccines and 6 days or longer after inactivated vaccines.

Recently, the 12th fiscal year (FY) 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter the "Subcommittee on Drug Safety") held on January 31, 2020 agreed to revise the package insert of vaccines on October 1, 2020 to lift, while maintaining the current restriction of 27 days or longer as the dosing interval between live vaccines, the current restrictions on intervals for any other combinations of vaccines.

This section will outline the revision of Precautions of the package insert which is scheduled on October 1, 2020 concerning the time intervals between administrations of different vaccines.



<Note>

- **For several days after vaccination, symptoms such as pyrexia or injection site swelling may appear. Absence of pyrexia, injection site swelling, or other symptoms indicative of impaired conditions should be ensured before vaccination even at intervals in line with the package insert.**
- **Simultaneous vaccination is acceptable when specifically permitted by the physician.**
- **For intervals for multiple dosing of the same vaccine, instructions in the package insert should be followed.**

2. Backgrounds of revision

The 34th Basic Policies Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council held on September 26, 2019 (hereinafter “the Basic Policies Subcommittee”) agreed upon including rotavirus vaccines in the scope of the routine immunization program as the course of action. This decision expanded the number of vaccines required in infancy. The Basic Policies Subcommittee also agreed that the restriction on dosing intervals should be reviewed to enforce the decision in terms of ensuring vaccination opportunities. Thereafter, the 36th Basic Policies Subcommittee held on December 23, 2019 discussed the proposed revision of the Routine Immunization Guidelines that would maintain the current 27 days or longer intervals between live injectable vaccines and place no restrictions regarding the dosing intervals for other combinations of vaccines (including live oral vaccines). Since the proposed revision would alter the extensively acknowledged rule, public comments were solicited. Then, on January 27, 2020, the 37th Basic Policies Subcommittee approved the revision of the guidelines to be implemented from October 1, 2020.

In response to this decision, the 12th FY 2019 Subcommittee on Drug Safety held on January 31, 2020 decided that revision of the package insert was necessary to lift restrictions on the intervals between dosing of different vaccines except for combinations of live injectable vaccines in line with the revision of the Routine Immunization Guidelines (Table 1). In light of these discussions and decisions, the MHLW issued the notification entitled Revisions of Precautions in Package Inserts concerning the Dosing Intervals between Different Vaccines (PSEHB/PSD 0228 No.5 by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated February 28, 2020) to instruct marketing authorization holders of vaccines to revise the package inserts of their products on October 1, 2020.

Table 1. Revision of package insert (model example)

For live injectable vaccines — Revised language is underlined.

Current	Revision
Precautions of Dosage and Administration Dosing intervals with other vaccine preparations A person recently administered with another live vaccine usually should receive this vaccine at least 27 days apart. A person recently administered with an inactivated vaccine should usually receive this vaccine at least 6 days apart. Conditionally, this product may be vaccinated simultaneously when the physician considers it necessary.	Precautions of Dosage and Administration Dosing intervals with other live vaccines (injection) A person recently administered with another live vaccine (injection) usually should receive this vaccine at least 27 days apart. (deleted) Simultaneous vaccination This product may be vaccinated simultaneously with other vaccines when the physician considers it necessary.

For inactivated vaccines and live oral vaccines — Revised language is underlined.

Current	Revision
Precautions of Dosage and Administration Dosing intervals with other vaccine preparations A person recently administered with another live vaccine usually should receive this vaccine at least 27 days apart. A person recently administered with an inactivated vaccine should usually receive this vaccine at least 6 days apart. Conditionally, this product may be vaccinated simultaneously when the physician considers it necessary.	Precautions of Dosage and Administration (deleted) Simultaneous vaccination This product may be vaccinated simultaneously with other vaccines when the physician considers it necessary.

3. Closing remark

From October 1, 2020, the Routine Immunization Guidelines will be amended and the package inserts of vaccines will be revised concerning the dosing intervals between different vaccines.

On the other hand, the current interval of 27 days or longer between live injectable vaccines will be retained. This should be noted among medical professionals who consider vaccination schedules. For multiple dosing of the same vaccine, a certain time interval should be placed between individual doses according to the dosage and administration or other related information in the package insert of the specific vaccine product.

MHLW/PMDA will continue to gather safety information on vaccines including suspected adverse reaction reports and to adopt safety measures. Alerting the vaccine recipients and reporting suspected adverse reactions to the vaccines by healthcare professionals are encouraged and appreciated.

[References]

- Materials of the 34th Basic Policies Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council
  https://www.mhlw.go.jp/stf/newpage_06937.html (only in Japanese)
- Materials of the 36th Basic Policies Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council
  https://www.mhlw.go.jp/stf/newpage_08589.html (only in Japanese)
- Materials of the 37th Basic Policies Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council
  https://www.mhlw.go.jp/stf/newpage_09097.html (only in Japanese)
- Materials of the 12th FY 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council
  https://www.mhlw.go.jp/stf/newpage_09224.html (only in Japanese)
- Revisions of Precautions in Package Inserts concerning the Dosing Intervals between Different Vaccines (PSEHB/PSD 0228 No.5 dated February 28, 2020)
  https://www.pmda.go.jp/files/000234162.pdf (only in Japanese)

2

Review of Contraindications including “patients with serious renal disorder” of Parenteral Nutrition Preparations and Amino Acid Preparations for Renal Failure

1. Introduction

General purpose parenteral nutrition preparations are divided into the following three types: Amino acid preparations, peripheral parenteral nutrition (hereinafter referred to as “PPN”) preparations, and total parenteral nutrition (hereinafter referred to as “TPN”) preparations, which are widely used to supplement water, electrolytes, amino acids under malnutrition or pre/post-surgery. Amino acid preparations contain amino acids. PPN preparations contain amino acids, glucose, electrolytes, etc. TPN preparations are divided into a basic solution and kit agent. The basic solution contains glucose, electrolytes, etc. The solution is used after being mixed with an amino acid preparation. Each of the parenteral nutrition preparations is contraindicated in “patients with serious renal disorder or patients with azotaemia” for the reason that urea, a metabolite of amino acids, remains for a long time, possibly leading to aggravation of the symptom, etc. and “patients with oliguria” for the reason that hyperkalaemia can be aggravated or induced, etc.

Also, amino acid preparations for hepatic failure were contraindicated in “patients with serious renal disorder” based on the same rationale as parenteral nutrition preparations because they were intravenous preparations containing amino acids, although they do not aim to control nutrition.

The contraindication in “patients with serious renal disorder” etc., in parenteral nutrition preparations or amino acid preparations for hepatic failure was revised based on the consideration at the 3rd FY 2020 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council held on June 15, 2020 (hereinafter referred to as the “Subcommittee on Drug Safety”), and the details are introduced below.

2. Background

As mentioned above, general purpose parenteral nutrition preparations were contraindicated in “patients with serious renal disorder.” The Japanese Society for Parenteral and Enteral Nutrition (the Japanese Society for Clinical Nutrition and Metabolism, at present) in June 2017 and the Japanese Society of Intensive Care Medicine in November 2017 submitted a request for review of the contraindication for general purpose parenteral nutrition preparations to the Ministry of Health, Labour and Welfare. They revealed that it was not clear whether the contraindication in “patients with serious renal disorder” included patients on dialysis or hemofiltration, leading to confusion due to lack of an established interpretation in clinical settings. Also, dialysis or hemofiltration removes low-molecular substances such as water, electrolytes, amino acids, etc. as well as uraemia substances in patients on these procedures. As the conditions of patients on dialysis or hemofiltration vary, multiple options for nutrition management are necessary. Moreover, the European guidelines state that administration of standard preparations is appropriate to most patients on dialysis with chronic kidney disease and also with some acute diseases when they receive parenteral nutrition therapy. Based on these facts, it was suggested that “patients on dialysis or on hemofiltration” be excluded from the “patients with serious renal disorder” in the contraindication.

In light of the requests from the above-mentioned academic societies, MHLW decided to consider a revision of the contraindication in “patients with serious renal disorder” in general purpose parenteral nutrition preparations and the contraindication in “patients with serious renal disorder” in amino acid preparations for hepatic failure for the same reason as general purpose parenteral nutrition preparations.

3. Considerations at Subcommittee on Drug Safety

(1) Exclusion of patients on dialysis or hemofiltration from “patients with serious renal disorder” in the contraindication

The results of the investigation of the statements in Japanese and overseas guidelines, statements in overseas package inserts, adverse reaction reports/studies or reports on measures etc. are as follows.

- Based on the purpose and urea removal capacity of dialysis and hemofiltration, it is reasonable to consider that an excessive volume of water, electrolytes, urea, etc. is properly controlled in patients on dialysis and hemofiltration
- Japanese and overseas guidelines recommend that patients on dialysis receive parenteral nutrition preparations or amino acid preparations with the standard composition.
- The preparations are not contraindicated in patients on dialysis or hemofiltration in overseas package inserts.
- As with parenteral nutrition preparations, when amino acid preparations for hepatic failure are administered to patients on dialysis or hemofiltration, it is reasonable to consider that excessive urea etc. would be properly controlled.

Based on these results, the Subcommittee on Drug Safety considered that it is acceptable to exclude patients on dialysis or hemofiltration from “patients with serious renal disorder” contraindicated in the package inserts of general purpose parenteral nutrition preparations and amino acid preparations for hepatic failure.

(2) Exclusion of patients on dialysis or hemofiltration from “patients with azotaemia” and “patients with oliguria” in the contraindication

It was also considered to be acceptable to exclude patients on dialysis or hemofiltration from “patients with azotaemia” and “patients with oliguria” contraindicated with general purpose parenteral nutrition preparations for the following reasons.

- “Patients with azotaemia” and “patients with oliguria” include “patients with serious renal disorder” in terms of the conditions.
- In the patients on dialysis or hemofiltration, it is considered that an excessive volume of water, electrolytes, urea, etc. caused by parenteral nutrition preparations would be properly controlled, as mentioned above.

(3) Risk management of patients on dialysis or hemofiltration

The volume of urea removed and accumulated varies depending on the dialysis method and patients’ conditions. Therefore, as risk management of patients on dialysis or hemofiltration, it was considered that the statement that “in patients with serious renal disorder on dialysis or hemofiltration or patients with azotaemia, the volume of water, electrolytes, or urea removed and accumulated varies depending on the dialysis method and patients’ conditions and initiation and continuation of administration should be determined after the patient’s condition is carefully checked based on an assessment of blood biochemistry, acid-base equilibrium, body-fluid balance, etc.” should be included in the Important Precautions section.

4. Closing remark

Healthcare professionals are required to understand the gist of this revision and to determine whether to administer parenteral nutrition preparations and amino acid preparations for renal failure after the dialysis method is confirmed and patients’ conditions are carefully checked if the preparations are an option. We will continue to cooperate for proper use of parenteral nutrition preparations and amino acid preparations for renal failure.

[References]

・Materials 1-1 to 1-4 of the 3rd FY 2020 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on June 15, 2020)

https://www.mhlw.go.jp/stf/newpage_11824.html (only in Japanese)

- Revision of Precautions (PSEHB/PSD Notification No. 0625-1 dated June 25, 2020)
  https://www.mhlw.go.jp/content/11120000/000643327.pdf (only in Japanese)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0008.html
  (translation of proposed revisions by PMDA)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated July 20, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Iopamidol

Branded name (name of company)	Iopamiron Inj. 300, Iopamiron Inj. Syringe 300 (Bayer Yakuhin, Ltd), and the others
Therapeutic category	X-ray contrast media
Indications	Cerebral angiography, aortography, angiocardiography (including pulmonary arteriography), etc.

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse Reactions Clinically Significant Adverse Reactions (newly added)

Contrast-induced encephalopathy: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, angiocardiography (including pulmonary artery angiography), and aortography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

[Under new instructions]

11. ADVERSE REACTIONS

11.1 Clinically Significant Adverse Reactions (newly added)

(Cerebral angiography, angiocardiography (including pulmonary artery angiography), and aortography)
Contrast-induced encephalopathy
Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 35-month period (April 2017 to February 2020)
Cases involving contrast-induced encephalopathy: 5 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 2 200 000
Japanese market launch: August 1986

Case

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
1	Male 70s	Cerebral angiography (diabetes mellitus, hypertension, hepatic cirrhosis, mitral valve incompetence, diabetic nephropathy, chronic kidney disease, intracranial aneurysm)	160 mL (300 mg/mL) 1 day	Contrast-induced encephalopathy	
				10 years before administration	Hemodialysis was initiated for chronic renal failure caused by diabetic nephropathy
				1 day before administration	Hemodialysis was performed.
				Day 1 of administration (Day of termination)	A guiding catheter was placed in the left vertebral artery. Coil embolization for unruptured basilar tip aneurysm (approx. 9 mm in size) was performed using double catheter technique. (Approx. 160 mL of iopamidol was used as a contrast medium) The operation was completed without any intraoperative complications. Although the patient experienced headache and vomited immediately after the operation, no local neurological manifestations were observed. Dexamethasone was administered for normal post-opoerative care. A few hours later, the patient experienced visual disturbances caused by visual field defect and mild consciousness disturbance.
				1 day after termination	Consciousness disturbance deteriorated further. Brain computer-assisted tomography confirmed left dominant residual contrast medium accompanied by edematous changes in the bilateral occipital lobe and thalamus. At this point, the patient was diagnosed with contrast-induced encephalopathy. Hemodialysis was performed immediately. Although the patient's consciousness disturbance almost completely disappeared quickly after dialysis, visual disturbances persisted.
				2 days after termination	The patient almost fully recovered from visual disturbance after second dialysis was performed. Diffusion-weighted MRI confirmed a hyperintensity area along the sulci of the left occipital lobe and a faint hyperintensity area in the left thalamus.
				1 week after termination	The patient was discharged from the hospital without sequelae.
	Concomitant drugs: no data available				

4
Revision of Precautions (No.315)

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 July 20, 2020.

1 X-ray contrast media
[1] Iodixanol
[2] Iohexol (preparations with indications of cerebral angiography)

Branded name	[1] Visipaque 270 Injection 20 mL, 50 mL, 100 mL, Visipaque 320 Injection 50 mL, 100 mL (GE Healthcare Pharma Ltd) [2] Omnipaque 140 Injection 50 mL, Omnipaque 180 Injection 10 mL, Omnipaque 240 Injection Syringe 100 mL (GE Healthcare Pharma Ltd), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Contrast-induced encephalopathy**: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1. Clinically Significant Adverse Reactions (newly added)**	(Cerebral angiography) Contrast-induced encephalopathy Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

2 X-ray contrast media
Iopamidol

Branded name	Iopamiron Inj. 300, Iopamiron Inj. Syringe 300 (Bayer Yakuhin, Ltd), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Contrast-induced encephalopathy**: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, angiocardiography (including pulmonary artery angiography), and aortography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1. Clinically Significant Adverse Reactions (newly added)**	(Cerebral angiography, angiocardiography (including pulmonary artery angiography), and aortography) Contrast-induced encephalopathy Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

3 X-ray contrast media

Iopromide

Branded name	Proscope 300 Syringe 50 mL, Proscope 300 Injection 20 mL (Alfresa Pharma Corporation), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	Disturbed consciousness, paralysis, aphasia, cortical blindness, or other contrast-induced encephalopathy symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, thoracic aortography, and angiocardiography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.
[Under New instructions]	
11. ADVERSE REACTIONS	(Cerebral angiography, thoracic aortography, and angiocardiography)
11.1 Clinically Significant Adverse Reactions (newly added)	Contrast-induced encephalopathy Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

4 X-ray contrast media

Iohexol (preparations with indications of cerebral angiography, angiocardiography (including pulmonary artery angiography), aortography, and angiocardiography of pediatrics (including pulmonary artery angiography))

Branded name	Omnipaque 140 Injection 50 mL, Omnipaque 180 Injection 10 mL, Omnipaque 240 Injection Syringe 100 mL (for urinary tract, CT) (GE Healthcare Pharma Ltd), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Contrast-induced encephalopathy**: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, angiocardiography (including pulmonary artery angiography), aortography, and angiocardiography of pediatrics (including pulmonary artery angiography). Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.
[Under New instructions]	
11. ADVERSE REACTIONS	(Cerebral angiography, angiocardiography (including pulmonary artery angiography), aortography, and angiocardiography of pediatrics (including pulmonary artery angiography))
11.1 Clinically Significant Adverse Reactions (newly added)	Contrast-induced encephalopathy Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

5 X-ray contrast media

Ioversol

Branded name	Optiray 240 Injection Syringe 100 mL, Optiray 320 Injection 20 mL (Guerbet Japan K.K.), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Contrast-induced encephalopathy**: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, angiocardiography, and aortography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	(Cerebral angiography, angiocardiography, and aortography) Contrast-induced encephalopathy Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

6 X-ray contrast media

Iomeprol

Branded name	Iomeron 300 Injection 20 mL, Iomeron 300 Injection Syringe 50 mL (Bracco-Eisai Co.,Ltd.), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Contrast-induced encephalopathy**: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, thoracic aortography, and angiocardiography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	(Cerebral angiography, thoracic aortography, and angiocardiography) Contrast-induced encephalopathy: Disturbed consciousness, paralysis, aphasia, cortical blindness, or other central nervous system symptoms may occur as a result of extracerebrovascular leakage of this drug in cerebral angiography, thoracic aortography, and angiocardiography. Minimum effective dosages should be administered and appropriate measures should be taken if any abnormalities are observed.

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 July, 2020)
◎: Products for which EPPV was initiated after July 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Posaconazole Noxafil for Intravenous Infusion 300 mg	MSD K.K.	July 21, 2020
◎	Lemborexant Dayvigo Tablets 2.5 mg, 5mg, 10 mg	Eisai Co., Ltd.	July 6, 2020
	Fluticasone propionate/formoterol fumarate hydrate Flutiform 50 Aerosol 56 puffs, 120 puffs	Kyorin Pharmaceutical Co.,Ltd.	June 29, 2020
	Semaglutide (genetical recombination) Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD	Novo Nordisk Pharma Ltd.	June 29, 2020
	Tolvaptan*1 Samsca tablets 7.5 mg, 15 mg, 30 mg, Samsca OD tablets 7.5 mg, 15 mg, 30 mg, Samsca granules 1%	Otsuka Pharmaceutical Co., Ltd.	June 29, 2020
	Landiolol hydrochloride*2 Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	June 29, 2020
	Levothyroxine sodium hydrate Thyradin-S I.V. Injection 200 μg	Aska Pharmaceutical. Co., Ltd.	June 29, 2020
	Delgocitinib Corectim Ointment 0.5%	Japan Tabacco Inc.	June 24, 2020
	Melatonin Melatobel granules 0.2% for pediatric	Nobelpharma Co., Ltd.	June 23, 2020
	Insulin lispro (genetical recombination) Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD Lyumjev Injection 100 U/mL	Eli Lilly Japan K.K.	June 17, 2020
	Insulin glargine (genetical recombination)/lixisenatide Soliqua Injection SoloStar	Sanofi K.K.	June 8, 2020
	Tepotinib hydrochloride hydrate Tepmetko Tablets 250 mg	Merck Biopharma Co., Ltd	June 1, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Nintedanib ethanesulfonate*3 Ofev capsules 100 mg, 150 mg	Boehringer Ingelheim Japan, Inc.	May 29, 2020
Darolutamide Nubeqa tablets 300 mg	Bayer Yakuhin Ltd	May 26, 2020
Trastuzumab deruxtecan (genetical recombination) Enhertu for intravenous drip infusion 100 mg	Daiichi Sankyo Co., Ltd.	May 25, 2020
Brolucizumab (genetical recombination) Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	May 25, 2020
Dotinurad Urece Tablets 0.5 mg, 1 mg, 2 mg	FUJIYAKUHIN Co., Ltd.	May 25, 2020
Cabozantinib malate Cabometyx tablets 20 mg, 60 mg	Takeda Pharmaceutical Company Limited.	May 22, 2020
Borofalan (^{10}B) Steboronine 9000 mg/300 mL for infusion	STELLA PHARMA CORPORATION	May 20, 2020
Tirabrutinib hydrochloride Velexbru Tablets 80 mg	Ono Pharmaceutical Co., Ltd.	May 20, 2020
Viltolarsen Viltepso Injection 250 mg	Nippon Shinyaku Co., Ltd.	May 20, 2020
Sodium zirconium cyclosilicate hydrate Lokelma 5 g/10 g powder for suspension (single-dose package)	AstraZeneca K.K.	May 20, 2020
Remdesivir Veklury for Intravenous Injection 100 mg	Gilead Sciences Inc.	May 11, 2020
Upadacitinib hydrate Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	April 24, 2020
Posaconazole Noxafil Tablets 100 mg	MSD K.K.	April 24, 2020
Lurasidone hydrochloride Latuda tablets 20 mg, 40 mg, 60 mg, 80 mg	Sumitomo Dainippon Pharma Co., Ltd.	April 22, 2020
Dinoprostone Propess vaginal inserts 10 mg	Ferring Pharmaceuticals Co., Ltd.	April 2, 2020
Mepolizumab (genetical recombination) Nucala for s.c. injection 100 mg	Glaxo Smith Kline K.K.	March 25, 2020
Dupilumab (genetical recombination) *4 Dupixent 300 mg Syringe for S.C. Injection	Sanofi K.K.	March 25, 2020
pH4-Treated normal human immunoglobulin*5 Privigen 10% I.V. Drip Infusion 5g/50mL, 10g/100mL, 20g/200mL	CSL Behring K.K.	February 21, 2020
Entrectinib*6 Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	February 21, 2020
Modafinil*7 Modiodal Tablets 100 mg	Alfresa Pharma Corporation	February 21, 2020
Doravirine Pifeltro Tablets 100 mg	MSD K.K.	February 17, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Insulin aspart (genetical recombination) Fiasp Injection FlexTouch, Fiasp Injection Penfill, Fiasp Injection 100 U/mL	Novo Nordisk Pharma Ltd.	February 7, 2020

*1 Improvement of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

*2 Tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) associated with sepsis

*3 Progressive fibrosing interstitial lung disease

*4 Chronic rhinosinusitis with nasal polyps (only in patients not adequately controlled with existing therapies)

*5 Agammaglobulinaemia or hypogammaglobulinaemia

*6 ROS1 fusion-positive, unresectable, advanced or metastatic non-small cell lung cancer

*7 Excessive daytime sleepiness associated with idiopathic hypersomnia