Pharmaceuticals and Medical Devices Safety Information

No. 409 April 2024

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) web page (https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.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 the MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.
This service is available only in Japanese.

Register here

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Pharmaceutical Safety Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

Pharmaceuticals and Medical Devices Safety Information

No. 409 April 2024

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

[Outline of Information]

5	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of March 31, 2024	23
	(Reference) Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)		Recently, based on the latest knowledge, precautions regarding “immune effector cell-associated neurotoxicity syndrome (ICANS)” have been included in the electronic package inserts of drugs and regenerative medical products which are used for the treatment of haematological malignancies.	26

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

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

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

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

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

Abbreviations

ACT	Activated Coagulation Time
ADR	Adverse Drug Reaction
CPB	Cardiopulmonary Bypass
ELD	Evaluation and Licensing Division
EPPV	Early Post-marketing Phase Vigilance
FFP	Fresh Frozen Plasma
FY	Fiscal Year
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
JCS	Japan Coma Scale
JDIIP	Japan Drug Information Institute in Pregnancy
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PED	Pharmaceutical Evaluation Division
PFSB	Pharmaceuticals and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
RMP	Risk Management Plan
SD	Safety Division
WG	Working Group

1

Utilization of Risk Management Plan (RMP) in Clinical Settings

1. Introduction

It is important to utilize the Risk Management Plan (hereinafter referred to as "RMP") to ensure proper use of drugs and minimize risks. RMPs are prepared to sort out, from the phase of development onward, the risks of drugs (information on adverse drug reactions, etc.) to be collected after marketing and to examine and implement activities to minimize the risks and collect information.

This section introduces the outline of overall RMPs and the utilization of RMPs in clinical settings. Please utilize this information in your clinical settings.

2. RMP

In principle, an RMP is prepared for each active ingredient and consists of three basic elements: Safety specifications, pharmacovigilance activities, and risk minimization activities. In addition, safety specifications consist of important identified risks, important potential risks, and important missing information. For these risks and information, how to "collect information (pharmacovigilance activities)" and how to "provide information (risk minimization activities)" are organized and provided in the RMP (Figure 1). Each activity is composed of two types of activities: Activities conducted commonly for all drugs (routine activities) and activities conducted individually based on the drug properties (additional activities). The RMP is not a fixed document, but it is a "living document" in which the benefit-risk balance is assessed periodically based on the implementation status and the contents of reports of pharmacovigilance activities and risk minimization activities, with revisions made as needed. It is expected that the ongoing comprehensive pharmacovigilance activities and risk minimization activities visualized by the RMP be widely shared among healthcare professionals including physicians and pharmacists and that the information be utilized, leading to further enhancement of post-marketing safety measures.

3. Utilization of RMP

(1) Summary of RMP

In order to understand the RMP of each drug, it is important to first look at the overall picture in Summary of RMP provided at the beginning of the RMP. In Summary of RMP, outlines of safety specifications (important identified risks, important potential risks, important missing information), pharmacovigilance activities, risk minimization activities, etc. are summarized altogether on one sheet, and a page containing details is displayed by clicking on an item or an activity. Therefore, this section plays a role as the table of contents of the RMP (Figure 2). By confirming whether safety specifications and additional risk minimization activities (activities specific to drugs) have been specified in Summary of RMP first of all, estimated risks and efforts to be made as safety measures can be grasped.

In safety specifications, in addition to "important identified risks" described in the package insert, "important potential risks," which are not necessarily included in the package insert, and "important missing information," in cases where information on the use of the drug is insufficient, are described. These should be referred to when conducting pharmacovigilance activities and risk minimization activities.

(2) RMP materials

As materials based on additional risk minimization activities, "Materials for healthcare professionals/materials for patients (hereinafter referred to as "RMP materials")" may be available for some drugs. These RMP materials are prepared when it is judged necessary to provide information to healthcare professionals and patients in accordance with the risks of individual drugs as a safety measure for the drug, in addition to the usual information provision through package inserts, etc. Among RMP materials, "materials for patients" may contribute to early detection of adverse reactions in patients, leading to prevention of the adverse reactions from becoming serious. Therefore, please utilize the RMP materials when providing explanations to patients. RMP materials in PDF format can be browsed on the PMDA website, and it is also possible to request the marketing authorization holder of the drug concerned to provide them directly. In addition, the RMP Marking is affixed to these materials to indicate that they are RMP materials (Figure 3).

(3) Acquisition of RMP and RMP materials

The RMP and RMP materials are posted on the PMDA website, and information on each product can be found at the following URL.

https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html
(only in Japanese)

How to find information on each product starting from the top page of the PMDA website is described here. (available only in Japanese)

[Method 1] Access to the top page of the PMDA website. → Menu for each of you → For Healthcare Professionals → Risk Management Plan (RMP) → List of RMP-submitted products. RMP materials can be browsed by clicking "Package insert, etc."

[Method 2] It is also possible to confirm the presence or absence of RMPs and RMP materials by searching individual drugs using the following method: Access to the top page of the PMDA website. → Search for package inserts, etc. → Search for information on prescription drugs.

4. Request for reporting adverse reactions, etc.

To determine post-marketing safety measures for drugs, adverse reactions, etc. reports from healthcare professionals are important sources of information. Your cooperation in Pharmaceuticals and Medical Devices Safety Information Reporting System is required in order to utilize the information for future safety measures such as revisions of package inserts and RMPs. Recently, “Study on Strategies to Utilize Adverse Drug Reaction Information From Healthcare Professionals" (research and development representative: Dr. Nariyasu Mano, Professor and Director of Department of Pharmaceutical Sciences, Tohoku University Hospital) was conducted as Research on Regulatory Science of Pharmaceuticals and Medical Devices Program granted from Japan Agency for Medical Research and Development, and "Draft Criteria for Information on Adverse Drug Reactions Which Healthcare Professionals Should Submit to the Regulatory Authority in Japan" was developed in order to enhance appropriate and prompt adverse reaction reporting from healthcare professionals. In that document, the adverse reactions which are listed as "important potential risks" in RMPs are described as the adverse reaction information to be reported. Characteristic adverse reactions occurring in pregnant women, breast-feeding women, children, persons with decreased renal function, and persons with decreased hepatic function, etc., which are represented by the descriptions in "important missing information" in RMPs, are also included. A drug safety information report or report on post-vaccination suspected adverse reactions can be prepared and submitted to the PMDA online at Report Reception Site of the PMDA website (Figure 4), and the report will be utilized for safety measures for drugs such as revisions of package inserts and RMPs. Please continue to cooperate in reporting adverse reactions, etc. related to those described in RMPs.

5. Conclusion

Through the accumulation of post-marketing use experience, utilization of RMP may reveal risks (adverse reactions) that had not been identified in the data including clinical studies conducted at the time of marketing approval. As a result of the fiscal year (FY) 2024 revision of dispensing fees, pharmaceutical management based on RMPs at pharmacies is now included for evaluation, and appropriate use of RMP in clinical settings is encouraged. Cooperation and understanding of healthcare professionals are requested for ensuring minimization of risks (adverse reactions) and proper use of drugs.

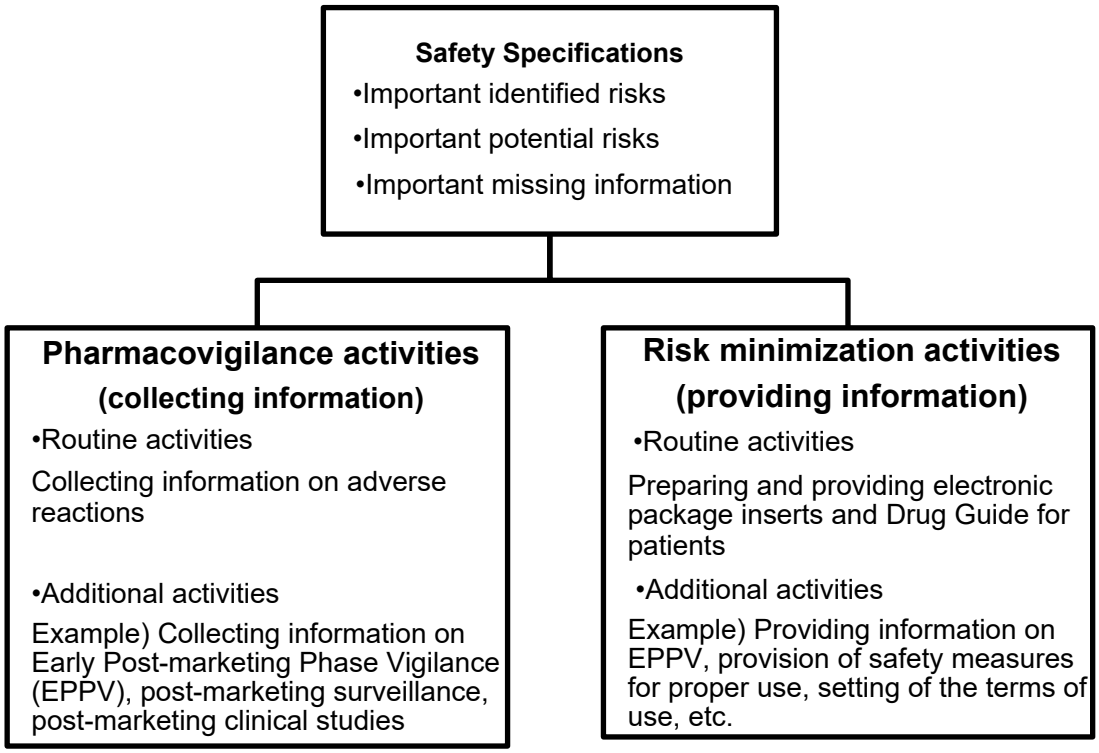
In addition, in order to provide a better understanding of RMP, the PMDA provides e-learning videos and the content “Learn about RMP in 3 Minutes” at the following URL.

https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0002.html (in Japanese)

https://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html (English webpage; e-learning videos, etc. are available only in Japanese)

Please view this content as well to deepen your understanding of the RMP and to proactively use the RMP in your clinical settings from now on.

(Figure 1)



(Figure 2)

(Appended Form 2)

Summary of Risk Management Plan (RMP) for ○○○○○○ (brand name)

Brand name	○○○○○○	**Active ingredient**	○○○○○○
Marketing authorization holder	○○○○○ Co., Ltd.	**Therapeutic category**	○○○○○○
Date of submission		DD/MM/YY	

1.1 Safety specifications		
[Important identified risks]	**[Important potential risks]**	**[Important missing information]**
(Name of a safety specification)	(Name of a safety specification)	(Name of a safety specification)

1.2. Efficacy specifications	
(Name of an efficacy specification)	

↓Pharmacovigilance activities based on the above

2. Summary of the pharmacovigilance activities
Routine pharmacovigilance activities
Additional pharmacovigilance activities
(Name of the pharmacovigilance activity)
3. Summary of the plans for surveillance and studies for efficacy
(Name of surveillance or study for efficacy)

↓ Risk minimization activities based on the above

4. Summary of the risk minimization plan
Routine risk minimization activities
Additional risk minimization activities
(Name of the risk minimization activity)

Please confirm the contents of each item in the text of the RMP

(Figure 3)

(Figure 4)

[References]

・Implementation of the Risk Management Plan: Pharmaceuticals and Medical Devices Safety Information (No. 300, issued in March 2013)
https://www.mhlw.go.jp/www1/kinkyu/iyaku_j/iyaku_j/anzenseijyouhou/300.pdf (in Japanese)
https://www.pmda.go.jp/files/000153064.pdf (in English)

・Publication of Risk Management Plan (RMP) Materials on the PMDA website: Pharmaceuticals and Medical Devices Safety Information (No. 367, issued in June 2019)
https://www.mhlw.go.jp/content/11120000/000570649.pdf (in Japanese)
https://www.pmda.go.jp/files/000231990.pdf (in English)

•Risk Management Plan Guidance (Joint PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No.0411-2, by the Directors of Safety Division and the Director of Evaluation and Licensing Division, Pharmaceuticals and Food Safety Bureau, MHLW dated April 11, 2012)
https://www.pmda.go.jp/files/000145482.pdf (in Japanese)
https://www.pmda.go.jp/files/000153333.pdf (in English)

•Application of the Risk Management Plan Guidance for Drugs (Joint PFSB/ELD Notification No.0826-3 and PFSB/SD Notification No. 0826-1, by the Director of Evaluation and Licensing Division and the Director of Safety Division, Pharmaceuticals and Food Safety Bureau,

MHLW dated August 26, 2014)
https://www.pmda.go.jp/files/000145421.pdf (only in Japanese)
•Marking on Materials Prepared and Distributed for Additional Risk Minimization Activities in Risk Management Plan (RMP) (Administrative Notice dated June 8, 2017)
https://www.pmda.go.jp/files/000218503.pdf (only in Japanese)
•Risk Management Plan templates, instructions and publication (PSEHB/PED Notification No. 0318-2 and PSEHB/PSD Notification No. 0318-1 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated March 18, 2022)
https://www.pmda.go.jp/files/000245412.pdf (in Japanese)
https://www.pmda.go.jp/files/000247589.pdf (in English)
•Partial Revision of "Publication of Risk Management Plan" (PSEHB/PED Notification No. 1029-1 and PSEHB/SD Notification No. 1029-1 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW dated October 29, 2018)
https://www.pmda.go.jp/files/000226448.pdf (only in Japanese)
•Risk Management Plan (RMP) (PMDA website)
https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0002.html (in Japanese)
https://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html (in English)

2

Revisions of PRECAUTIONS for Carvedilol and Bisoprolol

1. Introduction

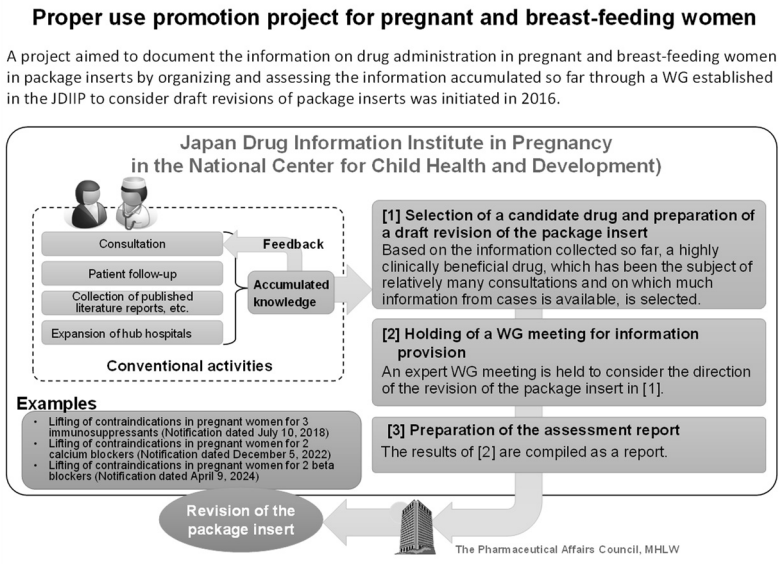
When drugs are used during pregnancy, attention must be paid to the effects on the fetus as well as on the mother. On the other hand, due to difficulties with obtaining safety information on drug use during pregnancy, women who are receiving drug therapy for pre-existing diseases may choose to avoid pregnancy or to discontinue taking prescribed necessary medications, which is an undesirable behavior. In addition, there are cases in which women who used drugs without realizing that they are pregnant become concerned about continuation of the pregnancy.

In 2005, the Japan Drug Information Institute in Pregnancy (hereinafter referred to as “JDIIP”) was established in the National Center for Child Health and Development by the MHLW to collect and assess the latest scientific evidence on the effects of drugs on mothers and fetuses. Based on these data, the JDIIP has provided consultations for women who are pregnant or who wish to become pregnant.

Since 2016, we have been engaged in a project to promote the documentation of information on drug use in pregnant women, etc. in package inserts by organizing and assessing the information accumulated so far by the JDIIP. In this project, a working group (hereinafter referred to as “WG”) composed of experts has been established. The WG selects a candidate drug, organizes and evaluates the information accumulated so far, and compiles the draft revision of the package insert for the drug as a report (Figure 1).

Recently, the language concerning contraindications, etc. for carvedilol, bisoprolol fumarate and bisoprolol (hereinafter, both active ingredients together are referred to as “bisoprolol”) among β blockers has been revised based on the deliberation in the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as “the Subcommittee on Drug Safety”). This section will introduce the details of the revision.

(Figure 1)



2. Details of the review by the WG

Carvedilol was approved for marketing in Japan for the indication of essential hypertension, renal parenchymal hypertension, angina pectoris, chronic heart failure due to ischaemic heart disease or dilated cardiomyopathy, and tachycardiac atrial fibrillation. However, a decrease in the corpus luteum count and an increase in skeletal anomalies have been reported at approximately 900-fold the clinical dose in studies in rats before pregnancy and in early pregnancy, and the safety has not been established for administration during pregnancy in humans. Therefore, administration of carvedilol to “pregnant women or women who may be pregnant” has been contraindicated since the marketing approval of the brand name product.

Bisoprolol was approved for marketing in Japan for the indication* of essential hypertension, angina pectoris, ventricular extrasystoles, chronic heart failure due to ischaemic heart disease or dilated cardiomyopathy, and tachycardiac atrial fibrillation. However, foetal toxicity (fatality, growth restriction) and neonatal toxicity (developmental toxicity, etc.) have been reported in animal studies. Therefore, administration of bisoprolol to “pregnant women or women who may be pregnant” has been contraindicated since the marketing approval of the brand name product.

On the contrary, a clinical need of β-blockers including carvedilol and bisoprolol (hereinafter referred to as “these drugs”) in pregnant women with chronic cardiac failure is considered to exist, and the need is increasing due to reasons such as increased cases of delayed childbearing and improvement of prognosis of the patients with congenital heart disease. On the other hand, taking into account that β blockers which can be administered to pregnant women at present (atenolol, propranolol, labetalol, etc.) are not indicated for chronic cardiac failure, with consideration also given to the clinical positioning of these drugs in Japanese guidelines with regard to the indications other than chronic cardiac failure, the clinical need of these drugs in pregnant women is considered to exist. Therefore, the appropriateness of contraindicating these drugs to pregnant women, etc. was investigated by the WG. A report was compiled stating that pregnant women or women who may be pregnant may be deleted from the CONTRAINDICATIONS sections in the package inserts for these drugs and that it is appropriate to add precautions that these drugs should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks.

(*) Bisoprolol fumarate is indicated for essential hypertension, angina pectoris, ventricular extrasystoles, chronic heart failure due to ischaemic heart disease or dilated cardiomyopathy, and tachycardiac atrial fibrillation.
Bisoprolol is indicated for essential hypertension and tachycardiac atrial fibrillation.

3. Deliberation by the Subcommittee on Drug Safety

Based on the deliberation by the WG and the investigation results by the PMDA in response to the WG report, the 16th FY 2023 Subcommittee on the Drug Safety held on March 26, 2024 concluded that the package inserts of these drugs may be revised as follows:

- “Pregnant women or women who may be pregnant” should be deleted from the CONTRAINDICATIONS section in the package insert, and a cautionary statement that “these drugs should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks.” should be added to the Pregnant Women section.
- In addition to the above precaution, a precaution should be issued that appropriate measures should be taken if any abnormalities are observed, with mothers, foetuses, and neonates monitored when the drug is administered, as well as the provision of information regarding the events reported in the literature and adverse reaction reports.

4. Closing comments

The present revisions of the package inserts are not intended to allow the unconditional use of carvedilol and bisoprolol in pregnant women or women who may be pregnant, which has previously been uniformly prohibited. Physicians prescribing these drugs must carefully decide

whether to administer these drugs or not while closely monitoring the condition of the patient's disease and weighing the expected therapeutic benefits against the possible risks associated with the treatment. Healthcare professionals are requested to understand the purpose of the present revisions, and continued cooperation for proper use of these drugs would be appreciated.

5. Reference

•Proper use promotion project for pregnant and breast-feeding women
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/ninshin_00002.html
(only in Japanese)

• Materials 1-1 to 1-3 of the 16th FY 2023 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on March 26, 2024)
https://www.mhlw.go.jp/stf/newpage_38855.html (only in Japanese)

• Revision of PRECAUTIONS (PSB/PSD Notification No. 0409-1 dated April 9, 2024)
https://www.mhlw.go.jp/content/11125000/001242432.pdf (in Japanese)
English translation by the PMDA (April 9, 2024)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated March 28, April 9, 2024, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Andexanet alfa (genetical recombination)

Brand name (name of company)	Ondexxya for Intravenous Injection 200 mg (AstraZeneca K.K.)
Therapeutic category	Other agents relating to blood and body fluids
Indications	The reversal of the anticoagulant effect of a direct-acting factor Xa inhibitor (apixaban, rivaroxaban, or edoxaban tosilate hydrate) in patients experiencing life-threatening or uncontrolled bleeding

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Heparin resistance may be observed. When this drug is administered at the time of surgery/procedure where anticoagulation with heparin is necessary, the necessity of administration of this drug should be carefully determined.
The cases in which this drug was used in the perioperative setting and heparin resistance was observed have been reported in both Japan and overseas. Among them, cases have been reported in which the anticoagulant effect of heparin could not be sufficiently obtained, and the extra-corporeal circuit was obstructed by thrombus, resulting in serious outcomes.

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Unfractionated heparin Heparin sodium Heparin calcium Low-molecular-weight heparin Enoxaparin sodium Dalteparin sodium Parnaparin sodium	The anticoagulant effect of heparin may be attenuated, and heparin resistance may be observed.	In vitro data suggests that this drug acts on heparin-antithrombin III complex, and attenuates the anticoagulant effect of heparin.

15. OTHER PRECAUTIONS

(deleted)

15.1 Information Based on Clinical Use
Reference information

Number of the following cases (for which a causal relationship between the drug and event is reasonably possible) retrieved from the

cases collected in the PMDA's database for adverse drug reactions, etc. reports: Cases reported as an adverse drug reaction named "heparin resistance (PT)"; among the cases in which both andexanet alfa (genetical recombination) and heparin were administered to the same patient, cases occurred including episodes in the clinical course for which the possibility of heparin resistance could not be ruled out.

Cases involving heparin resistance: 10 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 3,300
Japanese market launch: May 2022

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 80s	Aortic dissection (atrial fibrillation, hypertension, cardiac tamponade, insomnia)	880 mg for 1 day	**Heparin resistance, poor prolongation of ACT, excessive intraoperative haemorrhage** Medical history: Congestive cardiac failure	
				Day 1 of administration	The consciousness level was 300 (JCS) when the patient was found, and it was 3 (JCS) when he was transported. The vital signs indicated shock due to cardiac tamponade resulting from acute type A aortic dissection. Haemorrhage volume/haematoma volume: Unknown. Assessment of haemorrhage: Acute haemorrhage in a critical site or organ (e.g., intrapericardial, intracranial or intraspinal) The patient took the last dose of apixaban for paroxysmal atrial fibrillation, and apixaban was discontinued with this dose (last dose: 2.5 mg). Administration of andexanet alfa (genetical recombination) was started to reverse the anticoagulant effect. Total dose of andexanet alfa (genetical recombination): 400 mg + 480 mg (880 mg) Drug suspension/discontinuation: No An aortic dissection with thrombosed false lumen was noted at the level from the aortic arch to the superior mesenteric artery. Because an ulcer-like projection was observed on the opposite side of three vessels, emergent total arch replacement was performed. After the initiation of emergency surgery, the cardiac tamponade was removed, and the vital signs stabilized. After infusion of heparin 18,000 U, the activated coagulation time (ACT) became 543 seconds, and a cardiopulmonary bypass (CPB) was started. Heparin 10,000 U was administered into the priming solution, but ACT decreased to 252 seconds after the CPB. Heparin 15,000 U was added, and cooling was temporarily stopped. ACT was measured again 3 minutes later, but no prolongation was observed with a value of 274 seconds. Heparin 10,000 U was added for suspected abnormal coagulation associated with dissection, and cooling was resumed. Considering the possibility of antithrombin III deficiency, lyophilized human antithrombin III concentrate 1,500 U was administered. After administration, ACT was prolonged to 322 seconds. Heparin 5,000 U and lyophilized human antithrombin III concentrate 1,500 U were additionally administered. ACT was confirmed to have been prolonged to 404 seconds. After 5,000 U of heparin was further added, circulatory arrest was performed. After the circulatory arrest, ACT decreased to 318 seconds, and heparin 1,000 U each was additionally administered. Despite additional administration of heparin, ACT remained 280 seconds. Therefore, lyophilized human antithrombin III concentrate 3,000 U was

					added, which prolonged ACT to 373 seconds. After termination of the circulatory arrest, heparin 10,000 U was added, and ACT increased to 423 seconds. Fresh frozen plasma (FFP) 2 U was administered, followed by administration of heparin 5,000 U. FFP and heparin were intermittently administered thereafter, and ACT was maintained at around 400 seconds. The CPB was uneventfully completed. Four and a half hours after the start of andexanet alfa (genetical recombination), excessive intraoperative haemorrhage was noted. The patient received massive blood transfusion (red blood cell preparation, plasma preparation, platelet preparation, 35 U) until the next day.
				1 day after termination of administration	Excessive intraoperative haemorrhage was resolving.
				16 days after termination of administration	Postoperatively, the patient was transferred to another hospital without any major complications associated with the surgery.

Laboratory test value

Test item (unit)	Day 1 of administration	1 day after termination of administration
Haemoglobin (g/dL)	12.5	8.7
White blood cell count (/mm^3)	6,400	9,100
Platelet count (10^4/mm^3)	18.1	11.3
PT-INR (sec)	1.02	1.16
APTT (sec)	25.0	43.5
Prothrombin time (sec)	12.2	13.9
D-dimer (μg/mL)	10.2	96.7
Serum creatinine (mg/dL)	1.15	1.00
Cholinesterase ([U]/L)	183	-

Suspected concomitant drug: Heparin sodium
Concomitant drugs: Apixaban, protamine sulfate

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>2</td><td>Female
90s</td><td>Haemorrhages
(Aortic dissection)</td><td>Unknown
for 1 day</td><td colspan="2">Poor prolongation of ACT
Medical history: Hypertension, cerebral infarction</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Day 1 of administration</td><td>The patient was diagnosed with Stanford type A acute aortic dissection, and she was subject to an emergency operation.
The patient had tamponade due to haemorrhages, which occurred while she was on treatment with 15 mg of edoxaban. Therefore, administration of andexanet alfa (genetical recombination) was initiated using method A (intravenous bolus administration of 400 mg of andexanet alfa (genetical recombination) at a rate of 30 mg/min followed by a continuous infusion of 480 mg at a rate of 4 mg/min for 2 hours). The surgery was started while andexanet alfa (genetical recombination) was being administered continuously.
Following administration of 15,000 units of heparin, prolongation of ACT was confirmed once, and a cardiopulmonary bypass was initiated. However, poor prolongation of ACT was soon observed, and administration of several additional doses of heparin (35,000 units in total) and antithrombin III preparation was required.
With consideration given to the possible impact by andexanet alfa (genetical recombination), administration of andexanet alfa (genetical recombination) was discontinued. Prolongation of ACT was attained thereafter.</td></tr>
<tr><td></td><td colspan="5">Laboratory test value
<table>
<tr><th></th><th>Initial value</th><th>After 19 minutes</th><th>After 31 minutes</th><th>After 46 minutes (concomitant use of ATIII)</th><th>After 66 minutes</th><th>After 100 minutes (43 minutes after discontinuation)</th></tr>
<tr><td>ACT (seconds)</td><td>243</td><td>196</td><td>289</td><td>446</td><td>274</td><td>677</td></tr>
</table></td></tr>
<tr><td></td><td colspan="5">Suspected concomitant drugs: Lyophilized human antithrombin III concentrate
Concomitant drugs: Heparin sodium, edoxaban tosilate hydrate, nitroglycerin, dopamine hydrochloride, dobutamine hydrochloride, phenylephrine hydrochloride, tranexamic acid, calcium chloride hydrate, propofol, midazolam, rocuronium bromide, remifentanil hydrochloride, fentanyl citrate, cefapirin sodium, dexmedetomidine hydrochloride</td></tr>
</table>

4

Revisions of PRECAUTIONS (No. 349)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated March 28, April 9, 2024.

1 Other agents relating to blood and body fluids

Andexanet alfa (genetical recombination)

Brand name Ondexxya for Intravenous Injection 200 mg (AstraZeneca K.K.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Heparin resistance may be observed. When this drug is administered at the time of surgery/procedure where anticoagulation with heparin is necessary, the necessity of administration of this drug should be carefully determined.
The cases in which this drug was used in the perioperative setting and heparin resistance was observed have been reported in both Japan and overseas. Among them, cases have been reported in which the anticoagulant effect of heparin could not be sufficiently obtained, and the extra-corporeal circuit was obstructed by thrombus, resulting in serious outcomes.

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

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Unfractionated heparin Heparin sodium Heparin calcium Low-molecular-weight heparin Enoxaparin sodium Dalteparin sodium Parnaparin sodium	The anticoagulant effect of heparin may be attenuated, and heparin resistance may be observed.	In vitro data suggests that this drug acts on heparin-antithrombin III complex, and attenuates the anticoagulant effect of heparin.

15. OTHER PRECAUTIONS
15.1 Information Based on Clinical Use

(deleted)

2 [1]Axicabtagene ciloleucel [2]Idecabtagene vicleuce [3]Tisagenlecleucel [4]Lisocabtagene maraleucel

Brand name
[1]Yescarta Intravenous Drip Infusion (Gilead Sciences K.K.)
[2]Abecma Intravenous Infusion (Bristol-Myers Squibb K.K.)
[3]Kymriah Suspension for Intravenous Infusion (Novartis Pharma K.K.)

	[4]Breyanzi Suspension for Intravenous Infusion (Bristol-Myers Squibb K.K.)
Other Precautions (newly added)	Occurrence of lymphoid neoplasm of CAR-positive T-cell origin has been reported in patients treated with another regenerative medical product containing CAR-expressing T-cells.

3 Antiarrhythmic agents
Bisoprolol fumarate

Brand name	Maintate Tablets 0.625 mg, 2.5 mg, 5 mg (Mitsubishi Tanabe Pharma Corporation), Bisoprolol Fumarate Tablets 0.625 mg “Sawai,” 2,5 mg “Sawai,” 5 mg “Sawai” (Sawai Pharmaceutical Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “Sandoz,” 2.5 mg “Sandoz,” 5 mg “Sandoz” (Sandoz K.K.), Bisoprolol Fumarate Tab. 0.625 mg “Teva,” 2.5 mg “Teva,” 5mg “Teva” (Teva Takeda Pharma Ltd.), Bisoprolol Fumarate Tablets 0.625 mg "Towa," 2.5 mg "Towa," 5 mg "Towa" (Towa Pharmaceutical Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “Nichi-iko,” 2.5 mg “Nichi-iko,” 5 mg “Nichi-Iko” (Nichi-Iko Pharmaceutical Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “Nissin,” 2.5 mg “Nissin,” 5 mg “Nissin” (Nissin Pharmaceutical Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “Meiji,” 2.5 mg “Meiji,” 5 mg “Meiji” (Me Pharma Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “DSEP,” 2.5mg “DSEP,” 5 mg ”DSEP” (Daiichi Sankyo Espha Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “JG,” 2.5 mg “JG,” 5 mg “JG” (Nihon Generic Co., Ltd.), Bisoprolol Fumarate Tablets 0.625 mg “ZE,” 2.5 mg “ZE,” 5 mg “ZE” (Zensei Pharmaceutical Co., Ltd.)
[Under new instructions] **2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)**	(deleted)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prior to administration of this drug, mothers and foetuses should be carefully monitored. In addition, neonates should be carefully monitored after birth. If any abnormalities such as hypoglycaemia, bradycardia, feeding intolerance, etc. are observed in neonates, appropriate measures should be taken. It has been reported that foetal growth restriction, neonatal hypoglycaemia, bradycardia, feeding intolerance, etc. were noted when pregnant women were exposed to β-blockers. In addition, foetal toxicity (fatality, growth inhibition) and neonatal toxicity (developmental toxicity, etc.) have been reported in animal studies (rats, rabbits) (safety margin[note)]: 58-fold in rat foetuses, 39-fold in rabbit foetuses, and 19-fold in rat neonates). Note) The values of the safety margins were calculated by comparing the maximum clinical dose of this drug, which is 5 mg, and the no observed adverse effect level using body surface area conversion in animal studies (human equivalent dose based on body surface area conversion).

4 Antiarrhythmic agents

Bisoprolol

Brand name	Bisono tapes 2 mg, 4 mg, 8 mg (Toa Eiyo Ltd.)
[Under new instructions]	
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)	(deleted)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prior to administration of this drug, mothers and foetuses should be carefully monitored. In addition, neonates should be carefully monitored after birth. If any abnormalities such as hypoglycaemia, bradycardia, feeding intolerance, etc. are observed in neonates, appropriate measures should be taken. It has been reported that foetal growth restriction, neonatal hypoglycaemia, bradycardia, feeding intolerance, etc. were noted when pregnant women were exposed to β-blockers. In addition, foetal toxicity (fatality, growth inhibition) and neonatal toxicity (developmental toxicity, etc.) have been reported in animal studies (rats, rabbits) (safety margin[note)]: 58-fold in rat foetuses, 39-fold in rabbit foetuses, and 19-fold in rat neonates). Note) The values of the safety margins were calculated by comparing the maximum clinical dose of bisoprolol fumarate, which is 5 mg, and the no observed adverse effect level using body surface area conversion in animal studies (human equivalent dose based on body surface area conversion).

5 Antiarrhythmic agents

Carvedilol

Brand name	Artist Tablets 1.25 mg, 2.5 mg, 10 mg, 20 mg (Daiichi Sankyo Co., Ltd.), Carvedilol Tablets 1.25 mg “Amel,” 2.5 mg “Amel,” 10 mg “Amel,” 20 mg “Amel” (Kyowa Pharmaceutical Industry Co., Ltd.), Carvedilol Tablets 1.25 mg “Sawai,” 2.5 mg “Sawai,” 10 mg “Sawai,” 20 mg “Sawai” (Sawai Pharmaceutical Co., Ltd.), Carvedilol Tablets 1.25 mg “Tanabe,” 2.5 mg “Tanabe,” 10 mg “Tanabe,” 20 mg “Tanabe” (Nipro ES Pharma co., Ltd.), Carvedilol Tablets 1.25 mg “Towa,” 2.5 mg “Towa,” 10 mg “Towa,” 20 mg “Towa” (Towa Pharmaceutical Co., Ltd.), Carvedilol Tablets 1.25 mg “Nipro,” 2.5 mg “Nipro,” 10 mg “Nipro,” 20 mg “Nipro” (Nipro ES Pharma co., Ltd.), Carvedilol Tablets 1.25 mg “DSEP,” 2.5 mg “DSEP,” 10 mg “DSEP,” 20 mg “DSEP” (Daiichi Sankyo Espha Co., Ltd.), Carvedilol Tablets 1.25 mg “JG,” 2.5 mg “JG,” 10 mg “JG,” 20 mg “JG” (Nihon Generic Co., Ltd.), Carvedilol Tablets 1.25 mg “Me,” 2.5 mg “Me,” 10 mg “Me,” 20 mg “Me” (Meiji Seika Pharma Co., Ltd.), Carvedilol Tab. 1.25 mg “NIG,” 2.5 mg “NIG,” 10 mg “NIG,” 20 mg “NIG” (Nichi-Iko Gifu Plant Co., Ltd.), Carvedilol Tablets 1.25 mg “TCK,” 2.5 mg “TCK,” 10 mg “TCK,” 20 mg “TCK” (Tatsumi Kagaku Co., Ltd.), Carvedilol Tablets 1.25 mg “VTRS,” 2.5 mg “VTRS,” 10 mg “VTRS,” 20 mg “VTRS” (Viatris Healthcare G.K.)
[Under new instructions]	
2. CONTRAINDICATIONS (This drug is	(deleted)

contraindicated to the following patients.)	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prior to administration of this drug, mothers and foetuses should be carefully monitored. In addition, neonates should be carefully monitored after birth. If any abnormalities such as hypoglycaemia, bradycardia, feeding intolerance, etc. are observed in neonates, appropriate measures should be taken. It has been reported that foetal growth restriction, neonatal hypoglycaemia, bradycardia, feeding intolerance, etc. were noted when pregnant women were exposed to β-blockers. In addition, a decrease in the corpus luteum count and an increase in skeletal anomalies (shortening of 13th ribs) have been reported at approximately 150-fold the clinical dose (300 mg/kg) using body surface area conversion in studies in rats before pregnancy and in early pregnancy.

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 March 31, 2024)
◎: Products for which EPPV was initiated after February 1, 2024

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	March 26, 2024
◎	Rifaximin Rifxima Tablets 200 mg	Aska Pharmaceutical Co., Ltd.	March 26, 2024
◎	Fenfluramine hydrochloride[*1] Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	March 26, 2024
◎	Efgartigimod alfa (genetical recombination)[*2] Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	March 26, 2024
◎	Baricitinib[*3] (1) Olumiant tablets 2 mg, (2) Olumiant tablets 4 mg	Eli Lilly Japan K.K.	March 26, 2024
◎	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Gobik Aqueous Suspension Syringes	The Research Foundation for Microbial Diseases of Osaka University	March 15, 2024
◎	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Quintovac Aqueous Suspension Injection	KM Biologics Co., Ltd.	March 14, 2024
◎	Semaglutide (genetical recombination)[*4] (1) Wegovy Subcutaneous Injection 0.25 mg SD, (2) Wegovy Subcutaneous Injection 0.5 mg SD, (3) Wegovy Subcutaneous Injection 1.0 mg SD, (4) Wegovy Subcutaneous Injection 1.7 mg SD, (5) Wegovy Subcutaneous Injection 2.4 mg SD	Novo Nordisk Pharma Ltd.	February 22, 2024

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Tenapanor hydrochloride Phozevel Tablets 5mg, 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	February 20, 2024
◎	Zilucoplan sodium Zilbrysq Syringe for S.C. Injections 16.6 mg, 23.0 mg, 32.4 mg	UCB Japan Co. Ltd.	February 16, 2024
◎	Concizumab (genetical recombination) Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	February 16, 2024
◎	Sacubitril valsartan sodium hydrate[*5] (1) Entresto Tablets 50 mg, (2) Entresto Tablets 100 mg, (3) Entresto Tablets 200 mg	Novartis Pharma K.K.	February 9, 2024
◎	Empagliflozin[*6] Jardiance Tablets 10 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 9, 2024
	pH4-treated acidic normal human immunoglobulin (subcutaneous injection) Cuvitru 20% S.C. Injection 2 g/10 mL, 4 g/20 mL, 8 g/40 mL	Takeda Pharmaceutical Company Limited	January 24, 2024
	Recombinant respiratory syncytial virus vaccine Arexvy Intramuscular Injection	GlaxoSmithKline K.K.	January 15, 2024
	Glucarpidase (genetical recombination) Megludase for Intravenous Use 1000	Ohara Pharmaceutical Co., Ltd.	January 4, 2024
	Bimekizumab (genetical recombination)[*7] Bimzelx Syringe for S.C. injection 160 mg, Bimzelx Autoinjector for S.C. injection 160 mg	UCB Japan Co. Ltd.	December 22, 2023
	Eltrombopag olamine Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	December 22, 2023
	Brexpiprazole[*8] Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	December 22, 2023
	Cefiderocol tosilate sulfate hydrate Fetroja for Intravenous Drip Infusion 1 g	Shionogi & Co., Ltd.	December 20, 2023
	Lecanemab (genetical recombination) Leqembi for Intravenous Infusion 200 mg, 500 mg	Eisai Co., Ltd.	December 20, 2023
	Difelikefalin acetate Korsuva IV Injection Syringe for Dialysis 17.5 μg, 25.0 μg, 35.0 μg	Maruishi Pharmaceutical Co., Ltd.	December 13, 2023
	Coronavirus (SARS-CoV-2) RNA vaccine[*9] Daichirona for Intramuscular Injection	Daiichi Sankyo Co., Ltd.	December 1, 2023
	Rozanolixizumab (genetical recombination) Rystiggo for S.C. Injection 280 mg	UCB Japan Co. Ltd.	November 28, 2023
	Rivaroxaban[*10] [1] Xarelto tablets 10 mg, [2] Xarelto fine granules 10 mg, [3] Xarelto OD tablets 10	Bayer Yakuhin, Ltd.	November 24, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	mg, [4] Xarelto dry syrup for pediatric 51.7 mg, [5] Xarelto dry syrup for pediatric 103.4 mg, [6] Xarelto tablets 2.5 mg		
	Epcoritamab (genetical recombination) Epkinly Subcutaneous Injection 4 mg, 48 mg	Genmab K.K.	November 22, 2023
	Efanesoctocog alfa (genetical recombination) Altuviiio Intravenous 250, 500, 1000, 2000, 3000, 4000	Sanofi K.K.	November 22, 2023
	Inclisiran sodium Leqvio for s.c. injection syringe 300 mg	Novartis Pharma K.K.	November 22, 2023
	Pertuzumab (genetical recombination)/ trastuzumab (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Phesgo Combination for Subcutaneous Injection MA, Phesgo Combination for Subcutaneous Injection IN	Chugai Pharmaceutical Co., Ltd.	November 22, 2023
	Coronavirus (SARS-CoV-2) RNA vaccine Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	November 1, 2023
	Pegaspargase Oncaspar I.V. Infusion 3750	Nihon Servier Co. Ltd.	October 2, 2023

*1 Concomitant therapy with antiepileptic drugs for epileptic seizures in patients with Lennox-Gastaut syndrome who are not sufficiently responsive to other antiepileptic drugs

*2 Chronic idiopathic thrombocytopenic purpura

*3 Polyarticular-course juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional treatments

*4 Treatment of obesity

The use is limited to patients with either hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not adequately responded to treatment with diet and exercise therapy and meet the following conditions:

・BMI of 27 kg/m^2 or greater in the presence of at least two obesity-related comorbidities

・BMI of 35 kg/m^2 or greater

*5 Addition of pediatric dosage indicated for chronic heart failure

*6 Chronic kidney disease

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

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

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

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

(Reference)

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

1. Introduction

Recently, based on the latest knowledge, precautions regarding “immune effector cell-associated neurotoxicity syndrome (ICANS)” have been included in the electronic package inserts of drugs and regenerative medical products which are used for the treatment of haematological malignancies.

2. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

(1) Disease concept

The definition of immune effector cell-associated neurotoxicity syndrome (hereinafter referred to as “ICANS”) in the guideline by the American Society for Transplantation and Cellular Therapy[1)] is as follows:

ICANS is a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.

(2) Causes

It is assumed that ICANS may occur as a result of increased vascular permeability by inflammatory cytokines, blood-brain barrier breakdown, and increased cerebrospinal fluid cytokines and in some cases it leads to cerebral edema.[2)]

(3) Diagnosis and management

Diagnosis of ICANS is based on clinical findings, and the symptoms include tremor, confusion, agitation, and seizures. Dysphasia, hesitant speech and deterioration in handwriting are prominent and can progress to expressive and receptive aphasia.[1) 2)]

Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as administration of corticosteroids should be taken.

3. Conclusion

Healthcare professionals are requested to pay sufficient attention to the occurrence of ICANS following administration of relevant drugs or regenerative medical products.

Reference Literature

1) D.W. Lee, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019; 25: 625-638.
2) P. J. Hayden et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022; 33:259-275.