Pharmaceuticals and Medical Devices Safety Information

No. 341 March 2017

Table of Contents

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

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Pharmaceuticals and Medical Devices Safety Information

No. 341 March 2017

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

[Outline of Information]

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
AKI	Acute kidney injury
ARF	Acute renal failure
EPPV	Early Post-marketing Phase Vigilance
GAD	General Affairs Division
HPB	Health Policy Bureau
JADER	Japanese Adverse Drug Event Report
KDIGO	Kidney Disease Improving Global Outcomes
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MIC	Ministry of Internal Affairs and Communications
PDCA	Plan-do-check-act
PED	Pharmaceutical Evaluation Division
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PTP	Press-Through Package
SCr	Serum creatinine
SD	Safety Division
TERMS	Thalidomide Education and Risk Management System

1

Revisions of Proper Control Procedures for Revlimid/Pomalyst (RevMate)

Active ingredient	(1) Lenalidomide Hydrate (2) Pomalidomide
Brand name (name of company)	(1) Revlimid Capsules 2.5 mg and 5 mg (Celgene K.K.) (2) Pomalyst Capsules 1 mg, 2 mg, 3 mg, and 4 mg (Celgene K.K.)
Therapeutic category	Antineoplastics – Miscellaneous
Indications	(1) Relapsed or refractory multiple myeloma Myelodysplastic syndrome associated with a chromosome 5q deletion (2) Relapsed or refractory multiple myeloma

1. Introduction

Lenalidomide hydrate and pomalidomide (hereinafter referred to as “Revlimid, etc.”) belong to a drug class referred to as immunomodulators, and are thalidomide derivatives known to cause teratogenicity in humans. Given that teratogenicity was observed in trials where pregnant animals were administered Revlimid, etc., caution should be exercised when handling these drugs as they may possibly cause teratogenicity in humans as well.

Based on the above, similar to Thalidomide Education and Risk Management System (TERMS) established for thalidomide, proper control procedures for Revlimid/Pomalyst (RevMate) have been formulated as strict control procedures aimed at preventing fetal drug exposure. Healthcare professionals, patients, patients’ family members, etc. involved in Revlimid, etc. are requested to adhere to RevMate.

2. Incidents of Administration Errors of Revlimid, etc. in 2016

The Ministry of Health, Labour and Welfare (MHLW) issued a notification on “Handling of In-hospital Prescription of Thalidomide, Lenalidomide, and Pomalidomide” (Joint Health Policy Bureau (HPB)/General Affairs Division (GAD) Notification No. 0804-1 and Pharmaceutical Safety and Environmental Health Bureau (PSEHB)/Safety Division (SD) Notification No. 0804-3, by the Director of GAD, HPB, and the Director of SD, PSEHB, MHLW, dated August 4, 2016; hereinafter referred to as “the Notification”) as a new precaution given that an incident of administration error of Revlimid was reported in July 2016 in a medical institution. Administration errors have occurred after the Notification was issued as well, and 5 incidents of administration errors have been reported in FY 2016 (Please refer to **Table 1**). No serious health damages have been observed in any of the patients affected by these administration errors, and none of the patients were pregnant women or women with reproductive potential.

Table 1. Incidents of Administration Errors of Revlimid and Pomalyst

Issue date	Information of patients administered the product by error (age, sex)	Location of incident (Hospital ward, outpatient ward, etc.)	Process	Cause	Health damage	Preventative measures adopted by facility
July 2016	60s, male	Hematology ward (Hospitalized patient)	○Revlimid was delivered by error and administered to a different patient in the ward by error ○The package of the drug for the patient administered by error the product was not labeled with the patient's name ○Revlimid was dispensed in the package without the patient name label, and this was administered by error to a different patient ○The nurse who came for rounds discovered Revlimid on the bedside floor, uncovering the administration error	○The patient's name was not labeled on the drug package for the patient ○While procedures for delivering lenalidomide products was in place, it was not complied with ○Nurses who were solely responsible for delivering drugs were not shared the patient's administration information	No health damage	○When delivering lenalidomide products, will not simultaneously deliver drugs to other patients ○Confirm the patient's identity when delivering drugs ○Educate hospital ward nurses about RevMate
October 2016	60s, male (Patient himself)	Mixed hospital ward with surgery, gastroenterology, etc. departments (Hospitalized after visiting on an outpatient basis)	○Prescribing physician instructed change in prescription of Pomalyst to Revlimid when the patient was admitted to the hospital ○Based on the prescribing physician's comment "Change in prescription of "Lyrica only", the nurse returned Pomalyst, which was brought in by the patient, to the patient's family ○After the nurse administered Revlimid to the patient, the family delivered Pomalyst for the following day and the patient took Pomalyst the next day ○Pharmacist who confirmed drugs brought in discovered this error	○The notes by the physician in the electronic medical record was unclear ○Lack of education for nurses in regards to drugs	No health damage	○Create a record for actual administration ○2 people, a nurse and a pharmacist, will manage from dispensing the drug to administration and confirming the number of remaining drugs
October 2016	70s, male (Patient himself)	Mixed hospital ward with surgery, gastroenterology, etc. departments (Hospitalized after visiting on an outpatient basis)	○Dosage of Revlimid decreased due to onset of adverse drug reactions (ADR) ○On the first day prescription was changed, the dosage prior to the change was administered due to mistaken guidance from the nurse ○The pharmacist discovered the mistake when confirming the remaining drugs	○Inadequate confirmation of prescription change	Vomiting (non-serious)	○Create a record for actual administration ○2 people, a nurse and a pharmacist, will manage from dispensing the drug to administration and confirming the number of remaining drugs
December 2016	60s, female	Hematology ward (Hospitalized patient)	○Revlimid was administered by error to a different patient in the same room as the patient who was originally supposed to be administered the product ○After administration, a different nurse discovered the error when confirming the administration	○Both patients had just been hospitalized, and the name and face had yet to be recognized ○Failed to confirm patient/drug ○Delivered Revlimid by removing it from the kit	Sense of discomfort in stomach area	○Information shared during director meeting ○Thorough confirmation of patient/drug ○Administration to Revlimid and Pomalist patients will be initiated by pharmacists, and double checks will be performed by pharmacists and nurses
February 2017	80s, male	Hematology ward (Hospitalized patient)	○The nurse visited the patient's hospital room to deliver the drug, but the patient was absent; therefore, the nurse went to do other tasks with Revlimid at hand ○The nurse passed by another patient with multiple myeloma and gave the Revlimid she had kept to this patient by error causing administration error	○Both patients were multiple myeloma patients and their beds were next to one another causing the confusion ○Failed to confirm patient ○Performed other tasks while carrying the drug	No health damage	○Thorough dissemination of information on RevMate ○Thorough confirmation of patient

3. Revisions of RevMate

In light of the Notification and incidents of administration errors in 2016, the MHLW issued “Revisions to Safety Control Procedures for Use of Lenalidomide and Pomalidomide Products (request for precaution and dissemination of information to medical institutions)” (Joint PSEHB/Pharmaceutical Evaluation Division (PED) Notification No. 0215-1 and PSEHB/SD Notification 0215-1, by the Director of PED and the Director of SD, PSEHB, MHLW) on February 15, 2017 following the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 10th Meeting). The revisions made to RevMate are outlined as follows.

(1) Definition of terms
Newly defines “pharmacists involved in RevMate procedures” and “nurses in hospital wards”.
(2) Materials provided and education
a. Add educational materials for nurses in the Materials Provided.
b. Add “pharmacists involved in RevMate procedures” and “nurses in hospital wards” to the recipients of materials.
(3) As drug management during hospitalization
a. Must distinguish from other drugs.
b. Must verify patient identification when delivering the drug.
c. Must properly confirm patient’s compliance by retrieving Press Through Packages (PTP) sheets after use for example.
d. Should establish procedures regarding drug management when patients bring in drugs from other hospitals or when going home temporarily, etc.

4. Conclusion

Revisions made this time to RevMate are mainly in regards to handling of Revlimid, etc. during hospitalization. The RevMate specific website (http://www.revmate-japan.jp) (Only available in Japanese language) provides educational materials for healthcare professionals, etc. in addition to the revised RevMate. Healthcare professionals are requested to review safety management systems in their hospitals once again. We appreciate your continuous adherence to RevMate.

<References>

- Handling In-hospital Prescription of Thalidomide, Lenalidomide, and Pomalidomide (Joint HPB/GAD Notification No. 0804-1 and PSEHB/ SD Notification No. 0804-3 dated August 4, 2016)
(Only available in Japanese language)
http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000132483.pdf
- Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 10th Meeting in FY 2016)
(Only available in Japanese language)
http://www.mhlw.go.jp/stf/shingi2/0000149557.html
- Revisions to Safety Control Procedures for Use of Lenalidomide and Pomalidomide Products (request for precaution and dissemination of information to medical institutions) (Joint PSEHB/PED Notification No. 0215-1 and PSEHB/SD Notification 0215-1)
(Only available in Japanese language)
http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000151556.pdf
- RevMate® specific website
(Only available in Japanese language)
http://www.revmate-japan.jp

2

Research on Actual Status in Drugs and Medical Devices Safety Information Reporting System

1. Introduction

"Research on Awareness and Usage of Adverse Drug Reactions (ADR), etc., Reporting System Among Medical Institutions and Pharmacists and its Promotion" (Principal Investigator: Nariyasu Mano, Professor and Head of Department of Pharmaceutical Sciences, Tohoku University Hospital; hereinafter referred to as "the Research") is presently being conducted as part of Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Japan Agency for Medical Research and Development. The Research involves a survey on actual use of Drugs and Medical Devices Safety Information Reporting System, a system under our jurisdiction. The Research has been conducted for 3 years since 2014.

The Research is scheduled for completion in this fiscal year. This section will introduce the results provided by the research group.

2. Introducing the Results from the Research Group

- Members of the research group (authors)
  Nariyasu Mano[1], Taku Obara[1] ([1] Department of Pharmaceutical Sciences, Tohoku University Hospital)

- Introduction
  "Drugs and Medical Devices Safety Information Reporting System" is a system to collect post-marketing safety information on medical products from medical institutions. It was initiated in 1967 as an ADR monitoring system. At present, healthcare professionals, etc. are responsible for directly reporting information on health damages, etc. (i.e., ADR, infection, and malfunctions), which occur with use of drugs or medical devices in the healthcare environment to the Minister of Health, Labour and Welfare. Reporting should comply with the provisions of Article 68 Section 10 Paragraph 2 of the "Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals, Medical Devices, etc." In particular, healthcare professionals are requested to report "information (cases) deemed necessary to report in order to prevent the occurrence or spread of hygienic hazards" to the Minister of Health, Labour and Welfare (the PMDA acting as the contact point) (**Table 1**), and cases for which a causal relationship with drugs are unclear can be reportable as such information[1)]. While such reported information is utilized for various safety measures, it is made available at the PMDA website in a database (JADER: Japanese Adverse Drug Event Report database) together with reported ADRs etc. from marketing authorization holders (MAHs).
  Regrettably, direct reports from medical institutions based on the Drugs and Medical Devices Safety Information Reporting System are very limited at present, and the Ministry of Internal Affairs and Communications (MIC) has issued several advisories to "ensure awareness of the purpose of the reporting system in medical institutions so that safety information reports to the Minister of Health, Labour and Welfare are duly implemented"[2), 3)].

Table 1. Information that should be reported according to “Drugs and Medical Devices Safety Information Reporting System”*

For the occurrence of ADR, infections or malfunctions with the use of pharmaceuticals, medical devices, regenerative medicine products, etc. (including malfunctions that may cause health damages for medical devices or regenerative medicine products, etc.), information (cases) deemed necessary to report in order to prevent the occurrence or spread of hygienic hazards. Refer to the following examples (cases) for specifics. Please note that cases are subject to reporting as well when a causal relationship to drugs, medical devices, regenerative medicine products, etc., is not necessarily clear.

[1] Fatal

[2] Disabilities

[3] Cases that may be fatal

[4] Cases that may lead to disabilities

[5] Cases requiring hospitalization or prolonging duration of hospitalization for treatment at the hospital or clinic (excluding cases noted in [3] and [4])

[6] Serious cases in accordance with cases noted in [1] to [5]

[7] Congenital disorders or abnormalities in later generations

[8] Occurrence of infectious disease cases suspected to occur due to the use of relevant drugs, medical devices, regenerative medicine products, etc.

[9] Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicine products, etc., those with the risk of occurrence of cases, etc. noted in [1] to [7]

[10] Besides the cases noted in [1] to [8], occurrence of cases which are not mild and could not be predicted based on the package insert, etc.

[11] Of the malfunctions that occur due to the use of relevant medical devices, regenerative medicines, etc., those with the risk of occurrence of cases noted in [10]

* Revisions in practices of reporting ADR, infections, and malfunctions from medical institutions, etc. regarding drugs, medical devices, or regenerative medical products” (PSEHB Notification No. 0325-4 by the Director of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated March 25, 2016 (http://www.pmda.go.jp/files/000211248.pdf)

■ Study on the status of operation of “Drugs and Medical Devices Safety Information Reporting System”

Considering the increase in ADR, etc. reports based on the Drugs and Medical Devices Safety Information Reporting System, the research group has conducted studies on actual usage of this system, “Survey on hospital pharmacists” and “Survey on pharmacy departments at medical institutions,” to understand the barriers when reporting such information based on this system.

1. Survey on hospital pharmacists[4)]

A survey using a self-completion questionnaire regarding drug safety evaluation was conducted on 45007 pharmacists who are members of the Japanese Society of Hospital Pharmacists. Of the analysis set consisting of 3845 valid respondents, the overall percentage of pharmacists who did not understand the Drugs and Medical Devices Safety Information Reporting System and the percentage of pharmacists who did not have experience of submitting reports from their institutions was 23.1% and 57.6%, respectively. The percentage of pharmacists who did not understand the system was relatively higher

among males, those younger, with no PhD, or with shorter years of work experience (Figure 1). On the other hand, the percentage of pharmacists who did not have experience of reporting from their institutions was relatively higher in females, those younger, with no PhD, with shorter years of work experience, or with fewer colleague pharmacists at work (Figure 2). A total of 39.9% of respondents stated that they did not submit reports from their institutions because “the relationship between the drug and ADR was unclear” (Figure 3). The percentage was consistent irrespective of the understanding of the system. Results of this survey revealed that ensuring awareness and clarification of the definition of cases for which reporting by the system is requested, by clarifying that cases can also be reportable from medical institutions under the system when the causal relationship between the use of the drug and the ADR or suspected ADR is unclear, for example.

Whether an event is an ADR will be determined by the PMDA or MAHs through the evaluation of causal relationships based on accumulated information as well as through the evaluation of a causal relationship for individual cases; therefore, it is not always necessary to clarify a causal relationship when collecting information. Therefore, an extensive ADR reporting is important, including cases with unclear causal relationships as well.

Clarification of the cases reportable from medical institutions is necessary due to the fact that it is difficult to determine what “information (cases) deemed necessary to report in order to prevent the occurrence or spread of hygienic hazards” refers to as stated in the PSEHB Notification No. 0325-4 by the Director of the PSEHB, MHLW, dated March 25, 2016. For example, with regard to reports from pharmaceutical manufacturers, specific seriousness criteria for reportability was detailed in the notification by the Director of SD, Pharmaceutical Affairs Bureau, MHLW dated June 29, 1992 “Criteria for seriousness classification of adverse drug reactions” (SD Notification No. 80). In SD Notification No. 80, seriousness of ADRs of liver, kidney, blood, hypersensitivity, respiratory tract, gastrointestinal tract, cardiovascular system, neuropsychiatric system, and metabolic electrolyte abnormalities were categorized into 3 grades (“Grade 1: Mild ADR,” “Grade 2: Neither serious nor mild ADR,” and “Grade 3: ADR considered serious, which may be fatal or has the risk of causing permanent dysfunction that hinders daily living depending on the patient’s predisposition or condition when pyrexia is observed”). The notification states that in addition to Grade 3 ADR cases, cases with ADRs, which are not noted in the precautions, should be reported when they are Grade 1 or 2 as well. Clarifying which cases should be reported by healthcare professionals may increase the number of reports submitted by medical institutions.

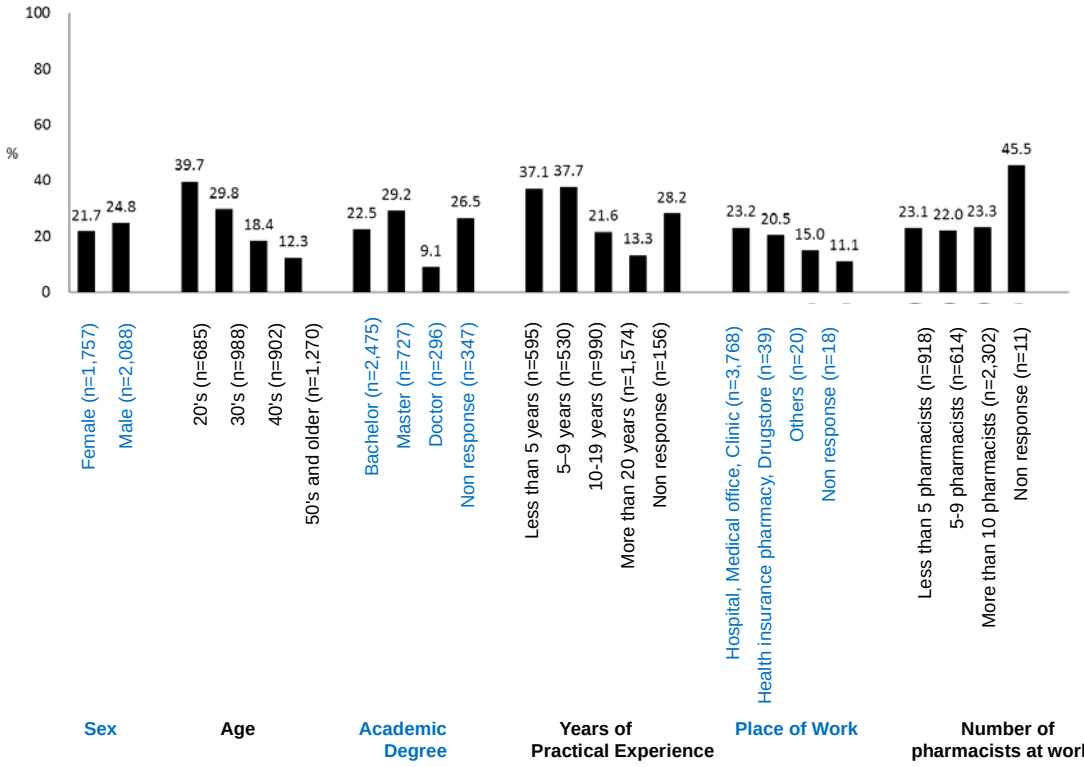


Figure 1.

Proportion of pharmacists who do not understand "Pharmaceuticals and Medical Device Safety Information Reporting System" Created from Reference literature 4)

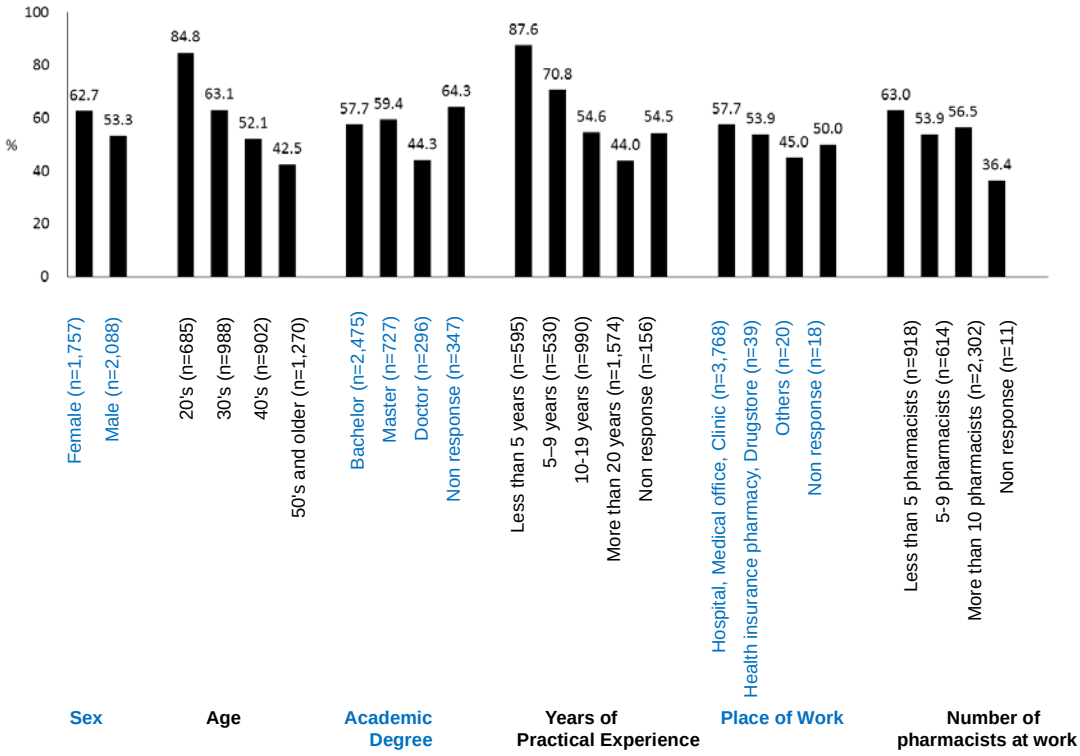


Figure 2.

Proportion of pharmacists without spontaneous reporting experience based on "Pharmaceuticals and Medical Device Safety Information Reporting System" Created from Reference literature 4)

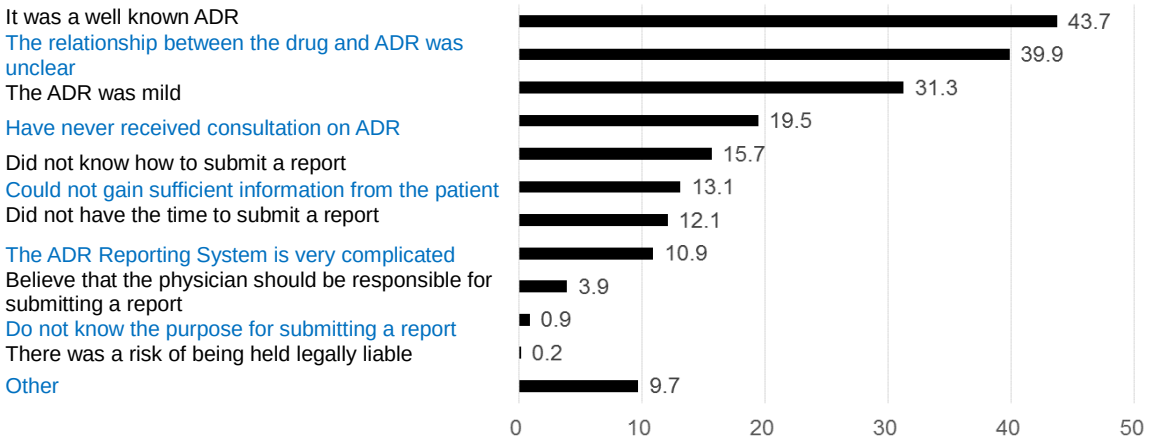


Figure3. Reasons for no experience submitting a spontaneous report based on this system
Created from Reference literature 4)

2. Survey on pharmacy departments at medical institutions[5)]

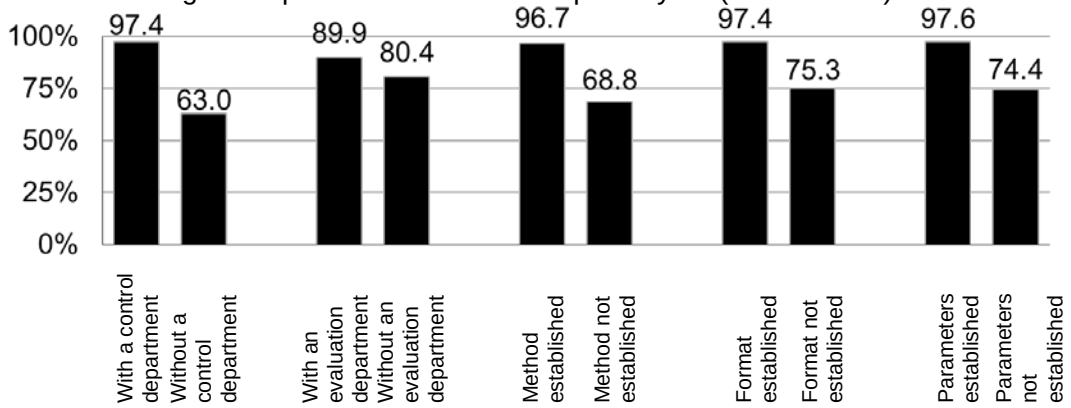
A survey using a questionnaire on collecting/managing ADR information in the hospital was conducted among a total of 167 pharmacy departments in medical institutions that are members of the Miyagi Hospital Pharmacists Association as well as national university hospitals. Of the analysis set consisting of 124 facilities, 62 facilities were aware of in-hospital occurrence of ADRs subject to reporting based on the Drugs and Medical Devices Safety Reporting System (facilities aware of ADR). The percentage of facilities aware of ADR was higher among facilities that have a specific department that centrally controls information of in-hospital ADRs (control department) and facilities that have established specific procedures ("methods," "formats," and "parameters" for example; specific procedure) for collecting information on in-hospital ADRs.

Fifty four of the 62 facilities aware of ADR or approximately 40% of the analysis set reported ADRs as medical institutions (reporting facilities). Among the reporting facilities, the percentage of those with the control department or specific procedure was high (Figure 4B).

In small facilities with no arrangements for a control department or specific procedure, the percentage of facilities aware of ADR as well as that of reporting facilities tended to be lower [5)].

As a method to collect/manage in-hospital ADR information within medical institutions, having a control department or establishing specific procedures may lead to the effective understanding of in-hospital ADRs within medical institutions as well as promote reporting based on the Drugs and Medical Devices Safety Reporting System[6), 7)].

a. ADR* occurring in-hospital as collected in the past 1 year (124 facilities)



b. In-hospital ADR as reported to MHLW (62 facilities in which ADR* have occurred in the past 1 year)

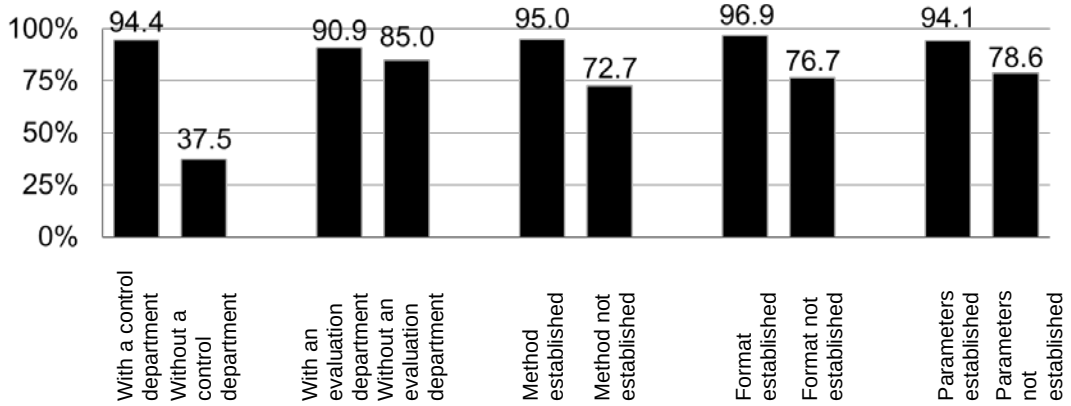


Figure 4. ADR occurring in-hospital and in-hospital ADR reported to the MHLW based on whether the facility has a control department and/or evaluation department and based on the establishment of a method, format, or parameters for reporting
*ADR subject to Drugs and Medical Devices Safety Reporting System

Created from Reference literature 5)

■ In future

It is anticipated that MAHs will be challenged in collecting information on incidents of ADRs or suspected ADRs in future due to the widespread use of generics and increase in home healthcare. Therefore, instead of relying solely on reports of ADR, etc. from MAHs, it will be desirable that all healthcare professionals, including physicians, dentists, and pharmacists, (including those that work at hospitals, dispensing pharmacies, and drugstores) appropriately understand and utilize this system.

■ Reference Literature

1) "Revisions in practices of reporting ADR, infections, and malfunctions from medical institutions, etc. regarding drugs, medical devices, or regenerative medical products" (PSEHB Notification No. 0325-4 by the Director of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated March 25, 2016
2) MIC, Recommendations Based on Administrative Evaluations/Monitoring Results Regarding Pharmaceuticals – Mainly focused on safety measures – dated June 2001 (Only available in Japanese language)
http://www.soumu.go.jp/main_sosiki/hyouka/010608_2.htm
3) MIC, Recommendations Based on Administrative Evaluations/Monitoring Results Regarding Widespread Use/Safety of Pharmaceuticals dated March 2013 (Only available in Japanese language)

http://www.soumu.go.jp/main_content/000213386.pdf
4) Nariyasu Mano, Research on Awareness and Usage of ADR, etc., Reporting System Among Medical Institutions and Pharmacists and its Promotion (H26-Pharmaceuticals B-General-004) FY 2014 Report on results of commissioned work dated March 2015
5) Taku Obara, Hiroaki Yamaguchi, Masaki Matsuura, Naoto Nakagawa, Yuriko Murai, Fumito Tsuchiya, Mitsukazu Kitada, and Nariyasu Mano; Study on collection/ management/reporting of in-hospital ADR information. Journal of Japanese Society of Hospital Pharmacists. 2017; 53: 73-77.
6) Yumi Niinuma; ADR information collected from guidance records for drug management. The Pharmaceuticals Monthly. 58: 2837-2841, 2016.
7) Naoto Nakagawa, Kanehiko Hisamichi, and Nariyasu Mano. Collecting active ADR information. The Pharmaceuticals Monthly. 58: 2833-2836, 2016.

3. Conclusions

ADR reporting from medical institutions based on the Drugs and Medical Devices Safety Information Reporting System is an integral part of safety measures as well as ADR reporting from MAHs. The MHLW intends to strive for enhanced implementation of the system based on the latest knowledge derived from the Research. We would appreciate active reporting of information on ADRs etc. under the Drugs and Medical Devices Safety Information Reporting System by healthcare professionals.

3

Revision of Precautions (No. 282)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated February 14, 2016.

1 Psychotropics

(a) Hydroxyzine hydrochloride
(b) Hydroxyzine pamoate

Brand name	(a) Atarax Tablets 10 mg, 25 mg, Atarax-P Parenteral Solution 25 mg/mL, 50 mg/mL (Pfizer Japan Inc.) (b) Atarax-P Powder 10%, Atarax-P Capsules 25 mg, 50 mg, Atarax-P Syrup 0.5%, Atarax-P Dry Syrup 2.5% (Pfizer Japan Inc.), and the others
Adverse reactions (clinically significant adverse reactions)	Acute generalized exanthematouspustulosis: Acute generalized exanthematouspustulosis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

2 Antineoplastics – Miscellaneous

Vemurafenib

Brand name	Zelboraf Tablet 240 mg (Chugai Pharmaceutical Co., Ltd.)
Important precautions	Acute kidney injury (AKI) may occur. Renal function tests should be performed before the start of, and periodically during, treatment.
Adverse reactions (clinically significant adverse reactions)	AKI: AKI may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or discontinuation of administration should be adopted.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of January 31, 2017)
◎: Products for which EPPV was initiated after January 1, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Emtricitabine /TenofovirAlafenamide Fumarate Descovy Combination Tablets LT and HT	Japan Tobacco Inc.	January 27, 2017
◎	DarunavirEthanolate/Cobicistat Prezcobix Combination Tablets	Janssen Pharmaceutical K.K.	January 4, 2017
	Carglumic Acid Carbaglu Dispersible Tablets 200 mg	Pola Pharma Inc.	December 22, 2016
	Canakinumab (Genetical Recombination) Ilaris for Subcutaneous Injection 150 mg*1	Novartis Pharma K.K.	December 19, 2016
	Eplerenone Selara Tablets 25, 50 mg*2	Pfizer Japan Inc.	December 19, 2016
	LomitapideMesilate Juxtapid Capsules 5, 10, 20 mg	Aegerion Pharmaceuticals Inc.	December 15, 2016
	Dienogest DINagest Tablets 1 mg, DINagest OD Tablets 1 mg*3	Mochida Pharmaceutical Co., Ltd.	December 2, 2016
	PasireotidePamoate Signifor LAR Kit for I. M. Injection 20, 40, 60 mg	Novartis Pharma K.K.	December 2, 2016
	Trafermin (genetical recombination) Regroth Dental Kit 600μg, 1200μg	Kaken Pharmaceutical Co., Ltd.	December 1, 2016
	Albutrepenonacog Alfa (Genetical Recombination) Idelvion I.V. Injection 250, 500, 1000, 2000	CSL Behring K.K.	November 29, 2016
	Rifaximin Rifxima Tablets 200 mg	Aska Pharmaceutical. Co., Ltd.	November 29, 2016
	Budesonide Zentacort Capsules 3 mg	Zeria Pharmaceutical Co., Ltd.	November 29, 2016
	Alogliptin Benzoate/Metformin Hydrochloride Inisync Combination Tablets	Takeda Pharmaceutical Company Limited	November 29, 2016
	Zoledronic Acid Hydrate Reclast for I.V. Injection 5 mg	Asahi Kasei Pharma Corporation	November 25, 2016

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Ponatinib Hydrochloride Iclusig Tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	November 21, 2016
Selexipag Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	November 21, 2016
Ixekizumab (Genetical Recombination) Taltz 80 mg Syringe for SC Injection, Taltz 80 mg Auto-Injector for SC Injection	Eli Lilly Japan K.K.	November 21, 2016
Grazoprevir Hydrate Grazyna Tablets 50 mg	MSD K.K.	November 18, 2016
Elbasvir Erelsa Tablets 50mg	MSD K.K.	November 18, 2016
Elotuzumab (Genetical Recombination) Empliciti I.V. Injection 300 mg, 400 mg	Bristol-Myers Squibb K.K.	November 18, 2016
Bilastine Bilanoa Tablets 20 mg	Taiho Pharmaceutical Co., Ltd.	November 18, 2016
Telmisartan/Amlodipine Besilate/ Hydrochlorothiazide Micatrio Combination Tablets	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2016
Idarucizumab (Genetical Recombination) Prizbind Intravenous Solution 2.5 g	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2016
Desloratadine Desalex Tablets 5 mg	MSD K.K.	November 18, 2016
Adapalene/Benzoyl Peroxide Epiduo Gel	Galderma S.A.	November 4, 2016
Brodalumab (Genetical Recombination) Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Hakko Kirin Co., Ltd.	September 30, 2016
Adalimumab (Genetical Recombination) Humira for SC Injection 40 mg syringe 0.8 mL, 40 mg syringe 0.4 mL, 80 mg syringe 0.8 mL[*4]	AbbVie GK	September 28, 2016
Aripiprazole Abilify Tablets 1 mg, 3 mg, 6 mg, 12 mg, OD Tablets 3 mg, 6 mg, 12 mg, powder 1%, oral solution 0.1%[*5]	Otsuka Pharmaceutical Co., Ltd.	September 28, 2016
Propranolol Hydrochloride Hemangiol Syrup for Pediatric 0.375%[*6]	Maruho Co., Ltd.	September 16, 2016
Progesterone OneCrinone 90 mg Progesterone Vaginal Gel	Merck Serono Co., Ltd.	September 7, 2016
Alirocumab (Genetical Recombination) Praluent Subcutaneous Injection pen 75 mg, 150 mg, Syringe 75 mg, 150 mg	Sanofi K.K.	September 5, 2016
Levodopa/Carbidopa Hydrate Duodopa enteral combination solution	AbbVie GK	September 1, 2016
Lacosamide Vimpat Tablets 50 mg, 100 mg	UCB Japan Co. Ltd.	August 31, 2016
Sodium Picosulfate Hydrate, Magnesium Oxide, Anhydrous Citric Acid Picoprep Combination Powder	Ferring Pharmaceuticals Co., Ltd.	August 31, 2016

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	Carfilzomib Kyprolis Intravenous Infusions 10 mg, 40 mg	ONO Pharmaceutical Co., Ltd.	August 31, 2016
	Nivolumab (Genetical Recombination) Opdivo Intravenous Infusions 20 mg, 100 mg*7	ONO Pharmaceutical Co., Ltd.	August 26, 2016
	Remifentanil Hydrochloride Ultiva Intravenous 2 mg, 5 mg*8	Janssen Pharmaceutical K.K.	August 26, 2016

*1 Familial mediterranean fever, Tumour necrosis factor receptor-associated periodic syndrome, Mevalonate kinase deficiency/Hyper IgD syndrome

*2 Chronic cardiac failure

*3 Improvement of pain in adenomyosis uteri

*4 Non-infectious intermediate, posterior and panuveitis

*5 Irritability associated with autism spectrum disorder in childhood

*6 Infantile haemangioma

*7 Radically unresectable or metastatic renal cell carcinoma

*8 Analgesia in maintaining general anesthesia of children

(Reference)

Terminology of “Acute Kidney Injury”

1. Introduction

Package inserts provide proper information based on latest knowledge to the healthcare field. The terminology “acute renal failure (ARF)”, which has been used in package inserts until now, will be changed to “acute kidney injury (AKI)” based on latest knowledge.

2. Background

Until now, “ARF” has been used in package inserts to describe conditions where there is a rapid decrease in renal function.

However, the definition of the disease “ARF” was not necessarily clearly defined in guidelines, etc. In recent years, “AKI” has instead been used because it is a well-defined disease concept and entails “ARF.” Therefore, the terminology used in package inserts was reviewed.

3. Recent Situations in Japan and Overseas

Traditionally, conditions associated with rapid decrease in renal function was perceived to be “ARF”. However, these conditions were widely known to have fatal risks even from an early or mild stage prior to lapsing into complete failure. Since the turn of 2000, International Society of Nephrology, American Society of Nephrology, National Kidney Foundation, and European Society of Intensive Care Medicine have started to propose the new disease concept of “AKI,” which includes kidney injuries at an earlier stage, instead of ARF. In addition, in 2012, Kidney Disease Improving Global Outcomes (KDIGO: International institution for kidney disease guidelines) proposed the KDIGO criteria (refer to the table below) for diagnosing AKI in the “KDIGO Clinical guidelines for AKI”[2)], which summarizes evidence gathered until now with regard to AKI.

Table. Definition and Stage Classification of AKI noted in the “KDIGO Clinical guidelines”

Definition	1. Serum creatinine (SCr) levels increase by ≥0.3 mg/dL within 48 hours 2. SCr levels increase by ≥×1.5 fold as compared to the basic values known or predicted within 7 days prior to this 3. Urine volume decreased to <0.5mL/kg/hour over 6 hours	
	SCr	**Urine volume**
Stage 1	1.5 to 1.9 fold compared to basic valueor Increase by ≥0.3mg/dL	<0.5 mL/kg/hour in 6 to 12 hours
Stage 2	2.0 to 2.9 fold compared to basic value	<0.5 mL/kg/hour in 12 hours or more
Stage 3	3.0 fold as compared to basic value or Increase by ≥4.0 mg/dL or Initiating renal replacement therapy or Decrease in eGFR <35mL/min/1.73m^2 in patients younger than 18 years old	<0.3 mL/kg/hour in 24 hours or moreor No urine in 12 hours or more

Note) Diagnose patients as AKI if they fulfill any of the definitions from 1 to 3. When categorizing severity of the disease by SCr and urine volume, adopt the one with higher severity.

In Japan, Japanese Society of Nephrology, the Japanese Society of Intensive Care Medicine, the Japanese Society for Dialysis Therapy, Japan Society for Blood Purification in Critical Care, and the Japanese Society for Pediatric Nephrology jointly formulated “2016 Clinical guidelines for AKI”[1)] in December 2016. This guideline indicates the usefulness of the disease concept “AKI” and KDIGO criteria in diagnosing the disease.

Furthermore, in other Japanese guidelines, etc., formulated in recent years, such as “2016

Clinical guidelines for kidney injury when administering pharmacological treatment for cancer," the terminology AKI has already been in use.

4. Conclusions

"AKI" is a well-defined disease concept and entails "ARF." Given that both Japanese and overseas guidelines have changed the terminology "ARF" to the terminology "AKI", the terminology in package inserts will also be changed from "ARF" to "AKI". Furthermore, related description updates may be necessary when changing the term "ARF" to "AKI".

<Reference literature>

1) 2016 Clinical guidelines for AKI (Tokyo Igakusha)
2) KDIGO Clinical guidelines for AKI; Kidney International Supplements (2012) 2, 1; doi: 10.1038/kisup.2012.1
3) 2016 Clinical guidelines for kidney injury when administering pharmacological treatment for cancer (Life Science Publishing Co., Ltd.)

List of corrections in the Pharmaceuticals and Medical Devices Safety Information No.340

Page	Revised	Original
4	Note for (1) Prescription errors of pneumococcal vaccines	
	"Pneumovax NP" (Pneumococcal Polysaccharide Vaccine, 23 Valent) intended for pediatric patients aged and above	"Pneumovax NP" (Pneumococcal Polysaccharide Vaccine, 23 Valent) intended for patients aged 2 and above