Pharmaceuticals and Medical Devices Safety Information

No. 344 June 2017

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

Available information is listed here

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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 344 June 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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Atrial tachycardia
ATP	Adenosine triphosphate
BP	Blood pressure
BUN	Blood urea nitrogen
Baso	Basophil
CRP	C-reactive protein
Cr	Creatinine
DC	Direct Current
EPPV	Early Post-marketing Phase Vigilance
Eos	Eosinophil
FT	Free thyroxine
FY	Fiscal year
GAD	General Affairs Division
HPB	Health Policy Bureau
HR	Heart rate
IT	Information technology
JCQHC	Japan Council for Quality Health Care
JP	Japanese Pharmacopoeia
Lym	Lymphocyte
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
Mono	Monocyte
Neu	Neutrophil
PAB	Pharmaceutical Affairs Bureau
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PTP	Press through packages
QA	Question and Answer
RI	Radioisotope
SD	Safety Division
SGML	Standard generalized markup language
SSSS	Staphylococcal scalded skin syndrome
TEN	Toxic epidermal necrolysis
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone
WBC	White blood cells
WHO	World Health Organization
XML	Extensible markup language
γ-GTP	gamma-glutamyl transpeptidase

1

Revision of Instructions for Package Inserts of Prescription Drugs

1. Introduction

Package inserts of prescription drugs are prepared by the marketing authorization holders (MAHs) of the drugs for the purposes of providing necessary information to healthcare professionals such as physicians, dentists, and pharmacists in order to ensure the safety for patients to whom drugs are applied and to promote the proper use of them based on the regulations of the Pharmaceuticals and Medical Devices Act.

For the preparation of package inserts, instructions were notified by the MHLW in 1997 as follows (Old Instructions).

- "Instructions for Package Inserts of Prescription Drugs" (PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau (PAB), MHW, dated April 25, 1997)
- "Instructions for Precautions of Prescription Drugs" (PAB Notification No. 607 by the Director General of PAB, MHW dated April 25, 1997)
- "Instructions for Package Inserts of Prescription Drugs" (PAB/Safety Division (SD) Notification No. 59 by the Director of SD, PAB, MHW, dated April 25, 1997)

Twenty years have passed since the issuance of the Old Instructions. Over the years, the circumstances surrounding medical care have undergone great changes such as advances in medical care, aging society, and the progress of IT technology. In the "Review of the Drug Regulatory Administration for Preventing Recurrence of Drug-induced Sufferings (final proposal)" in 2010, utilization of information service tools was proposed for reviewing the instructions for package inserts and for promptly disseminating the details of the revisions, in addition to reflecting the latest knowledge in package inserts and making prior confirmation mandatory. Also, in the Health and Labour Scientific Research conducted between 2008 and 2013, a concrete draft revision of the instructions was proposed.

With this background, a draft revision of the instructions was prepared based on the proposals from the Health and Labour Scientific Research and subsequent considerations. Based on a total of approximately 1000 opinions for Public Comment on the said draft revision (period: May 31 to July 15, 2016), the instructions have been revised with the "Instructions for Package Inserts of Prescription Drugs, etc. [Pharmaceutical Safety and Environmental Health Bureau (PSEHB) Notification No. 0608-1 by the Director of PSEHB, MHLW, dated June 8, 2017]" and the "Points to Consider regarding the Instructions for Package Inserts of Prescription Drugs, etc. " (PSEHB/SD Notification No. 0608-1 by the Director of SD, PSEHB, MHLW, dated June 8, 2017) (Revised Instructions).

2. Main Contents of Revision

The main contents of the revision are described below. Figure 1 compares the sections under "Precautions" between the Old and the Revised Instructions. For the image of the format of package inserts after the revision and the Revised Instructions themselves, please refer to Reference.

(1) Repeal of "Relative Contraindications"

The level of understanding of "Relative Contraindications" was investigated in a large-scale survey on package inserts in physicians and pharmacists in the Health and Labour Scientific Research conducted between 2008 and 2010. Approximately half of both, physicians and pharmacists, answered "Relative Contraindications are equivalent to Contraindications", but on the

other hand, about half of the professions answered “Relative Contraindications are equivalent to Careful Administration/Precautions For Co-Administration”, showing the current situation that the understanding of the positioning of this section varies among individuals. For this reason, it was decided that “Relative Contraindications” would be repealed and the precautions would be included in “Contraindication(s)” or in the “Patients with Complication or History of Diseases, etc.” of the “Precautions concerning Patients with Secific Backgrounds” section to be newly established (See (4)).

(2) Repeal of “Careful Administration”

It was decided that precautions for patients with specific backgrounds excluding contraindications would be integrated with the newly established section of “Precautions concerning Patients with Specific Backgrounds”, and as such, “Careful Administration” will be repealed. These precautions will be included in the section of “Patients with Complication or History of Diseases, etc.” or others under the “Precautions concerning Patients with Specific Backgrounds”. However, the precautions may be described in the “Precautions concerning Indication(s)”, “Precautions concerning Dosage and Administration”, or “Drug Interactions” depending on the contents.

(3) Repeal of “Geriatric Use”, “Use during Pregnancy, Delivery or Lactation”, and “Pediatric Use”

It was decided that precautions for patients with specific backgrounds excluding contraindications would be integrated with the newly established section of “Precautions concerning Patients with Specific Backgrounds”, and as such, “Geriatric Use”, “Use during Pregnancy, Delivery or Lactation”, and “Pediatric Use” will be repealed. These precautions will be listed in an appropriate section (“Patients with Reproductive Potential”, “Pregnant Women”, “Breast-Feeding Women”, “Pediatric Use”, and “Geriatric Use”) under the newly established “Precautions concerning Patients with specific backgrounds”.

(4) New Establishment of “Precautions concerning Patients with Specific Backgrounds”

To integrate precautions for patients with specific backgrounds excluding contraindications, “Precautions concerning Patients with Specific Backgrounds” will be newly established. Under this section, sections of “Patients with Complication or History of Diseases, etc.”, “Patients with Renal Impairment”, “Patients with Hepatic Impairment”, “Patients with Reproductive Potential”, “Pregnant Women”, “Breast-Feeding Women”, “Pediatric Use”, and “Geriatric Use” will be newly established.

(5) Serial Numbers of Sections

A fixed number in the form of “1.1” or the like will be given to all sections after “WARNINGS”. The serial No. of any related sections will be indicated mutually for cross reference. Also, when any sections required under the Revised Instructions are not applicable, these sections will be left blank and the section number as well as the section name will be skipped.

3. Enforcement Schedule

Enforcement of the instructions is scheduled on April 1, 2019. There will be a period of transitional measures until March 31, 2024 (Figure 2). During approximately 2 years until April 1, 2019 when the Revised Instructions will be enforced, modifications to deal with the Revised Instructions, such as changing the programming language from SGML to XML, will be made for the package insert notification/publication system of the PMDA so that the convenience of the package insert search system provided on the PMDA’s website will be enhanced. In addition, during the period of transitional measures of 5 years from April 1, 2019 to March 31, 2024, both package inserts based on the Old Instructions and those based on the Revised Instructions will exist in the clinical practices and this may cause problems. MAHs will be guided to promptly implement package inserts based on the Revised Instructions.

The instructions for package inserts of vaccines among prescription drugs are specified in the “Instructions for Package Inserts of Vaccines, etc.” (PAB Notification No. 20 by the Director of PAB, MHLW, dated January 13, 1999) and the “Instructions for Precautions of Vaccines, etc.” (PAB Notification No. 21 by the Director of PAB, MHLW, dated January 13, 1999), and as such, these instructions will be revised separately. The instructions for vaccines will be issued preceded by

implementation of Public Comment as soon as the draft revision is formulated.

4. Closing Comments

This revision of the instructions for package inserts of prescription drugs will be the first revision in 20 years after the issuance of the Old Instructions. The familiar format will be modified. This revision of the instructions has been formulated based on opinions previously submitted from the clinical practices to the MHLW and lessons learned from past drug-induced sufferings. It will contribute more to the convenience of users. It is particularly intended for issues such as elimination of overlapping descriptions within package inserts and consolidation of related sections that are described separately in various places, about which many opinions have been collected. Among them, precautions, etc. for patients requiring attention for administration can be checked easily by referring to the "Precautions concerning Patients with specific backgrounds". In addition, serial numbers will be given to sections so that information needed will be checked faster.

Package inserts based on the Revised Instructions will be used in the clinical practices on and after April 1, 2019. Until that time, the MHLW will disseminate the Revised Instructions on various scenes in a careful manner. It is requested that healthcare professionals cooperate to understand the Revised Instructions for their smooth implementation.

5. References

PMDA HP

(Home > Post-marketing Safety Measures > Consultation for Safety Measures & Implementation [for MAHs] > Related Notifications)

- "Instructions for Package Inserts of Prescription Drugs, etc." (PSEHB Notification No. 0608-1 dated June 8 2017 issued by the Director of the PSEHB, MHLW dated June 8, 2017)

  http://www.pmda.go.jp/files/000218446.pdf (only available in Japanese language)

- "Points to Consider regarding the Instructions for Package Inserts of Prescription Drugs, etc." (PSEHB/SD Notification No. 0608-1 by the Director of SD, PSEHB, MHLW, dated June 8 2017)"

  http://pmda.go.jp/files/000218448.pdf (only available in Japanese language)

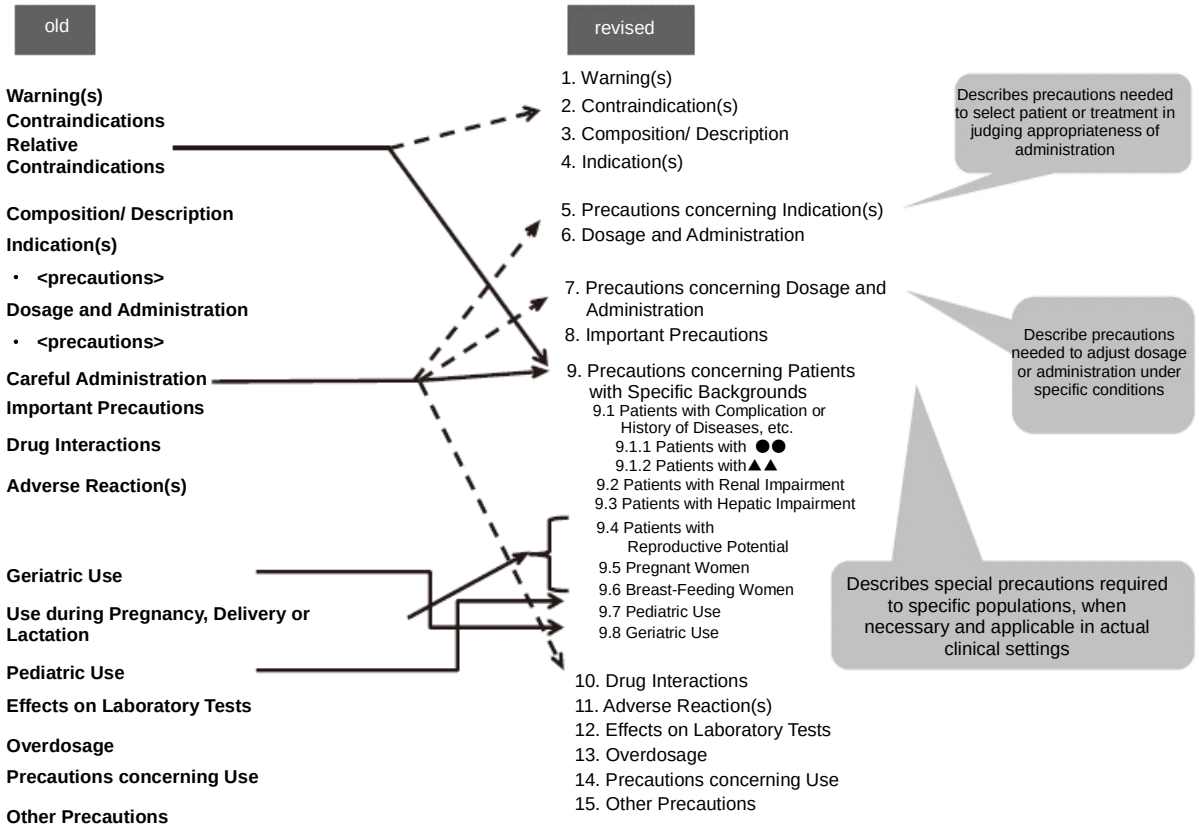

Figure 1 Comparison of old and revised package inserts

(Note) Arrows indicate corresponding items under the new guidance. Exceptions may apply.

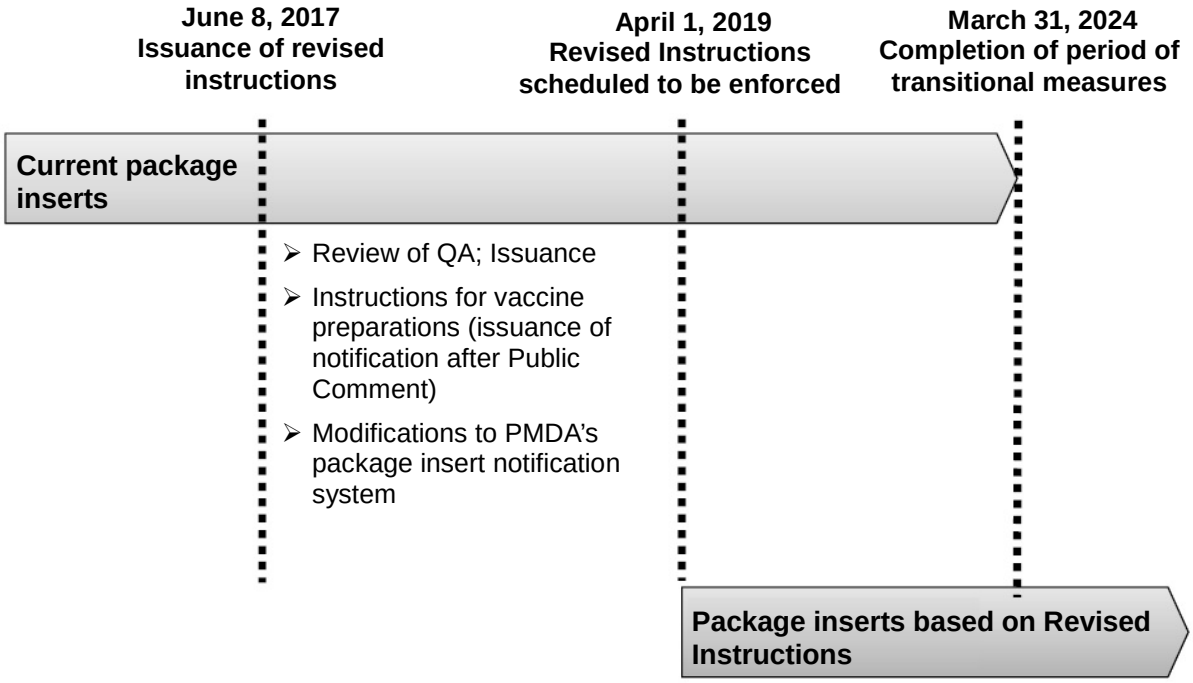

Figure 2 Schedule of Enforcement of Instructions for Package Inserts

Reference: Image of Package Insert Format based on Revised Instructions

STANDARD COMMODITY CLASSIFICATION NUMBER. OF JAPAN

**Revised XX 20XX (Version XX, ○○)

THERAPEUTIC CLASSIFICATION

STORAGE:

SHELF LIFE:

	●mg	▲ mg
MARKETING AUTHORIZATION NUMBER		
DATE OF INITIAL MARKETING IN JAPAN	XX 20XX	XX 20XX

Nonproprietary name, standard name, or name specified in Japanese Pharmacopoeia (JP)

REGULATORY CLASSIFICATION

Prescription drug Note)

Name of Product

Note) Caution - Use only based on a prescription of a physician, etc.

1. WARNINGS

2. CONTRAINDICATIONS (Do not use in the following patients.)

3. COMPOSITION/DESCRIPTION
 3.1 Composition
 < Tabular form >
 3.2 Product description
 < Tabular form >

4. INDICATIONS

5. PRECAUTIONS CONCERNING INDICATIONS

6. DOSAGE AND ADMINISTRATION

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

8. IMPORTANT PRECAUTIONS

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNRDS
 9.1 Patients with complication or history of diseases, etc.
 9.2 Patients with Renal Impairment
 9.3 Patients with Hepatic Impairment
 9.4 Patients with Reproductive Potential
 9.5 Pregnant Women
 9.6 Breast-Feeding Women
 9.7 Pediatric Use
 9.8 Geriatric Use

10. INTERACTIONS
 10.1 Contraindications For Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors

 10.2 Precautions For Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors

11. ADVERSE REACTIONS
 11.1 Clinically Significant Adverse Reactions
 11.1.1○○
 11.2 Other Adverse Reactions

	≥○%	0.1 to <○%	<0.1 %	Frequency unknown

12. INFLUENCE ON LABORATORY TESTS

13. OVERDOSAGE

14. PRECAUTIONS CONCERNING USE

15. OTHER PRECAUTIONS
  15.1 Information Based On Clinical Uses

  15.2 Information Based On Nonclinical Studies

16. PHARMACOKINETICS
  16.1 Blood Level

  16.2 Absorption

  16.3 Distribution

  16.4 Metabolism

  16.5 Excretion

  16.6 Patients with Specific Backgrounds

  16.7 Drug-Drug Interactions

  16.8 Others

17. CLINICAL STUDIES
  17.1 Efficacy And Safety

  17.2 Post-marketing Surveillance, etc.

  17.3 Others

18. PHARMACOLOGY
  18.1 Mechanism of Action

  18.2 ○○ Action

19. PHYSICOCHEMICAL PROPERTIES

20. PRECAUTIONS CONCERNING HANDLING

21. CONDITIONS FOR APPROVAL

22. PACKAGING

23. REFERENCES

24. REFERENCE REQUEST/ CONTACT INFORMATION

25. PRECAUTION CONCERNING HEALTH INSURANCE BENEFITS

26. MARKETING AUTHORIZATION HOLDER, etc.

2

Precautions Concerning Recurrent and Similar Medical Accidents

1. Introduction

The MHLW and PMDA are analyzing information on medical accidents and near-miss events collected as a part of the Project to Gather Medical Near-Miss/Adverse Event Information and the Project to Gather and Analyze Pharmaceutical Near-Miss Events run by the JCQHC. The MHLW and PMDA also strive to caution healthcare professionals by issuing notifications on the prevention of medical accidents related to pharmaceuticals and medical devices and by preparing the PMDA Medical Safety Information.

However, as a result of recent analysis of cases reported to the JCQHC between January 1, 2016 and June 30, 2016, the occurrence of the following events that had been cautioned in the notifications or PMDA Medical Safety Information was confirmed.

Therefore, in addition to detailing confirmed recurrent incidents, this section will especially focus on “Incidents of mix-up of drugs attributable to similarity of nonproprietary names.”

2. Major Recurrent Accidents

- **Incidents of mix-up of drugs attributable to similarity of nonproprietary names**

  Since April 1, 2012, for drugs for which a generic is available, the premium for nonproprietary name prescriptions has been available for medical institutions, when a prescription is issued in the format in which the dosage form and content are added to the nonproprietary name, instead of the product name listed in the National Health Insurance reimbursement price list. With the start of nonproprietary name prescriptions by medical institutions, a number of near-miss events at pharmacies in relation to nonproprietary name prescriptions have been reported every year.

○ Incident report

Isosorbide Dinitrate Sustained-release Tablets 20 mg Sawai was processed and dispensed to a patient based on a nonproprietary name prescription for isosorbide mononitrate tablets 20 mg.

Nonproprietary name prescribed: Isosorbide mononitrate tablets 20 mg
Drug that should be dispensed: Isosorbide Mononitrate Tablets 20 mg Sawai
Wrong drug: Isosorbide Dinitrate Sustained-release Tablets 20 mg Sawai
*Mix-up accidents also have been reported when switching to their original drugs (Itorol Tablets 20mg, Frandol Tablets 20 mg respectively).

○ Preventative measures for recurrence adopted by the facility where the incident occurred

Measures were taken such as putting a display calling attention on the medicine shelf and making a list of drugs that can be easily mixed up for re-checking at the time of audit.

○ Combinations of drugs associated with frequent mix-up accidents

The table below lists the combinations of nonproprietary drug names associated with mix-up accidents caused by the name similarity in nonproprietary prescription identified among the near-miss accidents reported to JCQHC between January 1, 2012 and June 30, 2016.

1	Potassium L-aspartate Calcium L-aspartate hydrate
2	Amoxapine Amoxicillin hydrate
3*	Arotinolol hydrochloride Allopurinol
4	Estazolam Etizolam
5	Ebastine Epinastine hydrochloride
6	Potassium citrate / sodium citrate hydrate mixt Sodium ferrous citrate
7	Clobetasol propionate Clobetasone butyrate
8	Dihydroergotamine mesilate Dihydroergotoxine mesilate
9	Sultopride hydrochloride Sulpiride
10*	Cefcapene pivoxil hydrochloride hydrate Cefditoren pivoxil Cefdinir Cefpodoxime proxetil

11	Nisoldipine Nilvadipine
12	Betamethasone dipropionate Betamethasone butyrate propionate
13	Benidipine hydrochloride Manidipine hydrochloride
14*	Ranitidine hydrochloride Lafutidine
15	Labetalol hydrochloride Rabeprazole sodium
16*	Rabeprazole sodium Lansoprazole
17	Levocabastine hydrochloride Levofloxacin hydrate
18*	Ethyl loflazepate Lorazepam
19	Zinc oxide Zinc oxide
20*	Isosorbide mononitrate Isosorbide dinitrate

* indicates combinations for which 3 or more mix-up accidents have been reported.

○ Related notifications or precautions

1) Administrative Notice dated May 26, 2017
Summary of results of “Research on the Penetration of Standardized Prescription Format of Oral Drugs” funded by Health and Labour Sciences Research Grants Fiscal year (FY) 2015 (Research Project for Development of Community Medicine Infrastructures) (provision of information)
: http://www.pmda.go.jp/files/000218340.pdf (only available in Japanese language)
Appendix 1 Summary of results of “Research on the Penetration of Standardized Prescription Format of Oral Drugs” funded by Health and Labour Sciences Research Grants FY 2015 Research Project for Development of Community Medicine Infrastructures (led by Dr. Fumito Tsuchiya, Specially Appointed Professor, School of Pharmacy, International University for Health and Welfare, the principal researcher):
http://www.pmda.go.jp/files/000218341.pdf (only available in Japanese language)
Appendix 2:“Publication of Special Committee Final Report on Proper Format of Oral Drug Prescriptions” [Joint Health Policy Bureau (HPB) Notification No. 0129-3 and PFSB No. 0129-5, by the Director of HPB and by the Director of Pharmaceutical and Food Safety Bureau (PFSB), MHLW, dated January 29, 2010 (request for circulation)]:
http://www.pmda.go.jp/files/000218342.pdf (only available in Japanese language)
2) Administrative Notice dated May 26, 2017 “Submission of Clarifications to Inquiries (No. 11)”

http://www.pmda.go.jp/files/000218343.pdf (only available in Japanese language)

Preventative Measures by Prescription Format
For drug names in which risk of mix-up due to similarity is particularly concerned in oral drug prescriptions based on nonproprietary names, measures such as product names of original drugs or representative generics as additional note for reference to the extent that use of original drugs is not induced may be effective.
For the handling in the health insurance claim please refer to the Administrative Notice Communication dated May 26, 2017 “Submission of Details of Inquiries for Clarification (No. 11).”

3) JCQHC: Analysis table of near-misses at pharmacies
FY 2015 Annual Report: Near-Misses related to Nonproprietary Name Prescriptions Incidents of dispensing drugs with different ingredients from those for the drug prescribed based on the nonproprietary name
http://www.yakkyoku-hiyari.jcqhc.or.jp/pdf/analysis_table_2013_03.pdf (only available in Japanese language)
FY 2012 Annual Report: Near-Misses related to Nonproprietary Name Prescriptions
http://www.yakkyoku-hiyari.jcqhc.or.jp/pdf/analysis_table_2012_07.pdf (only available in Japanese language)

(3) Other recurrent and similar incidents

(Analysis results of cases reported to the JCQHC between January 1, 2016 and June 30, 2016)
The following chart is a list of medical accident information and recurrence of near-miss accidents, etc.

[Pharmaceuticals]

No.	Content	Preventative Measures for Recurrence and Related Notifications
1	Mix-up of vaccine preparations	The label should be checked before inoculation without fail. PMDA Medical Safety Information No. 40 “Precautions in the Handling of Vaccines” http://www.pmda.go.jp/files/000153533.pdf
2	Mistakes in administration of antirheumatic methotrexate preparations (antiantirheumatic drug)	・ The understanding for oral drugs with a special dosing regimen requiring a rest period (when the drug is not administered) should be ensured. ・ The date and time of dosing (i.e. dosing schedule) should be indicated in the space provided on the package sheet when the drug is dispensed. In addition, the package sheet should not be cut off when dispensing the drug and the patient should be instructed not to cut it off themselves. Joint Notification of HPB/GAD Notification No. 1020001, PFSB/GAD Notification No. 1020001, and PFSB/SD Notification No. 1020001 dated October 20, 2008” Handling for Prevention Against Misuse (Overdose) of Antirheumatic Methotrexate Preparations (calling attention)” http://www.pmda.go.jp/files/000145447.pdf (only available in Japanese language)

[Pharmaceuticals]

No.	Content	Preventative Measures for Recurrence and Related Notifications
		PMDA Medical Safety Information No. 6 “Precautions against Misuse (Overdose) of Antirheumatic Methotrexate Preparations” http://www.pmda.go.jp/files/000153959.pdf PMDA Medical Safety Information No.49 “Precautions against Misuse (Overdose) of Antirheumatic Methotrexate Preparations” (Part 2) http://www.pmda.go.jp/files/000217392.pdf

[Pharmaceuticals]

No.	Content	Preventative Measures for Recurrence and Related Notifications
3	Accidetal ingestion of PTP sheets	The following measures are implemented to prevent accidental ingestion of Press Through Packages (PTP) sheets: (1) sheets should not be cut into individual pieces when dispensing, administering, etc. drugs; (2) patients and family, etc. should be instructed about storage and administration methods (including supervision during oral administration of patients who are anticipated to have difficulty managing drug administration on their own); and (3) dispensing drugs as a one dose package as necessary after consultation with the prescribing physician. Joint Notification of HPB/GAD Notification No. 0915-2, PFSB/GAD Notification No. 0915-5, and PFSB/SD Notification No. 0915-1 dated September 15, 2010 "Preventative measures for accidental ingestion of PTP sheet (request for precaution and dissemination to medical institutions and pharmacies)" http://www.pmda.go.jp/files/000145758.pdf (only available in Japanese language)

[Medical Devices]

No.	Content	Preventative Measures for Recurrence and Related Notifications
1	Removal of tubes and lines	Before changing the patient's body position or moving the patient, make sure to carefully observe whether lines will be caught, and confirm whether infusion stands and drainage bags should be moved. PMDA Medical Safety Information No. 36 "Accidental Removal of Tubes and Lines" http://www.pmda.go.jp/files/000153760.pdf
2	Incorrect intubation of nasogastric tubes	After intubation, confirm the position of the tube by using multiple methods. (Confirmation of correct tube positioning may be difficult to determine by the whooshing sound alone.) PMDA Medical Safety Information No. 42 "Precautions in Handling of Nasogastric Tubes" http://www.pmda.go.jp/files/000153901.pdf

[Medical Devices]

No.	Content	Preventative Measures for Recurrence and Related Notifications
3	Errors in flow rate programming of infusion pumps	The indicated content of drip infusion may not be in the order as in the programming of infusion pumps. After the input, the displayed “flow rate” and “scheduled rate” and the indicated content should be re-checked. PMDA Medical Safety Information No. 21 “Precautions in flow rate programming of infusion pumps” http://www.pmda.go.jp/files/000153278.pdf
4	Erroneous connection of lines for drug solution administration	When more than one line is connected, all of the lines should be checked with a finger at the time of re-connection of lines for drug solution administration. PMDA Medical Safety Information No. 47 “Handling of Lines for Drug Solution Administration” http://www.pmda.go.jp/files/000207412.pdf

3. Requests to Healthcare Professionals

Preventative measures for recurrence and related notifications have been presented this time for each distinct recurrent incident. In addition to re-confirming the management structure within the facility, please refer to the aforementioned information when providing guidance to patients and families, etc.

Please also refer to “PMDA Medical Safety Information” for details of other incidents for which caution should be exercised as well as “Medical Safety Information” issued by JCQHC, which uses illustrations to alert caution.

(References)

1 MHLW: Survey on Safe Use of Pharmaceuticals and Medical Devices
http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000057965.html (only available in Japanese language)

2 PMDA: Survey Results on Safe Use of Pharmaceuticals, Medical Devices, and Regenerative Medicines
http://www.pmda.go.jp/safety/info-services/medical-safety-info/0004.html (only available in Japanese language)

3 PMDA Medical Safety Information
http://www.pmda.go.jp/english/safety/info-services/safety-information/0001.html

4 JCQHC: Medical Safety Information
http://www.med-safe.jp/contents/english/index.html

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated May 30, 2017, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Treprostinil

Brand name (name of company)	Treprost for Injections 20 mg, 50 mg, 100 mg, 200 mg (Mochida Pharmaceutical Co., Ltd)
Therapeutic category	Cardiovascular agents-Miscellaneous
Indications	Pulmonary arterial hypertension (WHO functional classification; Class II, III and IV)

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Hyperthyroidism: Hyperthyroidism may occur. Patients should be carefully monitored through a thyroid function test, etc. as necessary. If any abnormalities are observed, appropriate measures should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 2 years and 7 months (September 2014 to April 2017)
Cases related to hyperthyroidism: 2 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 140

Launched in Japan: September 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Female 40s	Pulmonary arterial hypertension (Chronic heart failure)	89ng/kg/min Unknown ↓ 61.4ng/kg/min Unknown ↓ Discontinued	Hyperthyroidism History of allergy: Amoxicillin hydrate (Symptom: Generalized rash) Past history: Endometrial cancer, asthma, Hashimoto's disease, catheter infection, right heart failure 10 years and 7 months before administration: Administration of epoprostenol sodium was started due to pulmonary arterial hypertension. Day 1 of administration: Continuous subcutaneous administration of treprostinil was started for switching. Day 16 of administration: The heart rate (HR) increased to 120-130 from the daytime. The rate was higher than 140 when

				the patient moved a little. Blood pressure (BP) was steadily at the level of 130 mmHg. There are no subjective palpitations. The patient visited this hospital and was suspected to have adenosine triphosphate (ATP) sensitive atrial tachycardia (AT). Considering the history of asthma, Direct Current (DC) defibrillation was performed. AT ceased with 50J × 1, 100J, but it recurred. After that, spontaneous cessation and recurrence were repeated, and therefore DC was considered ineffective. The patient was admitted to the hospital for drug therapy. BP: 132/88 mmHg. HR: 109. Body temperature: 36.3°C. Enlargement of thyroid, elastic hard, and mobility were present. Pain was absent. The level of free thyroxine (FT_4) was high. Acute aggravation of Hashimoto's disease. Subacute thyroiditis was considered negative. Silent thyroiditis or drug-induced state was suspected. Oral administration of Lugol solution (50 mg in iodine equivalent) was started. Day 18 of administration: Thyroid hormone tended to decrease with oral administration of Lugol solution. AT was due to hyperthyroidism. HR94. Day 21 of administration: Thyroid blood flow did not decrease, and therefore it was not consistent with thyroiditis. Treatment was started with thiamazole 10 mg. Day 24 of administration: The patient was discharged from the hospital. Day 39 of administration: The dose of treprostinil was reduced with the expectation of reduction of leg pain that occurred after switching epoprostenol to treprostinil, but no effect was seen. The patient was admitted to the hospital for the purpose of inserting a Hickman catheter to switch back to epoprostenol. Day 40 of administration: (day of discontinuation) After insertion of the Hickman catheter, epoprostenol sodium was started. 2 days after discontinuation: AT did not recur and thyroid hormone also decreased, and consequently the patient was discharged from the hospital.
	Concomitant medications: sildenafil citrate, bosentan hydrate			

Laboratory Examination

Day of examination	20 days before administration	Day 16 of administration	Day 17 of administration	Day 18 of administration	Day 24 of administration	Day 36 of administration	Day 40 of administration
FT_4 (ng/dL)	1.51	5.99	-	5.27	3.85	2.4	2.2
FT_3 (pg/mL)	1.6	8.48	-	7.35	5.26	3.33	2.29
TSH (μIU/mL)	0.887	0.018	-	0.016	< 0.01	< 0.01	< 0.01
TSH receptor antibody (IU/L)	-	< 0.3	-	-	-	-	-
Antithyroid peroxidase antibody (anti-TPO antibody) (IU/mL)	-	-	380	-	-	-	-
Anti-thymoglobuline antibody (IU/mL)	-	-	32	-	-	-	-

Day of examination	5 days after discontinuation	71 days after discontinuation	99 days after discontinuation	134 days after discontinuation
FT_4 (ng/dL)	1.77	1.27	1.08	1.07
FT_3 (pg/mL)	2.31	2.3	1.84	1.73
TSH (μIU/mL)	0.019	1.654	2.679	4.091

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
2	Female 10s	Pulmonary arterial hypertension (none)	61.6ng/kg/min for 15 days ↓ 71.3ng/kg/min for 8 days ↓ 73.8ng/kg/min for 8 days ↓ 76.2ng/kg/min for 32 days ↓ 86.1ng/kg/min for 20 days ↓ 90.96ng/kg/min Unknown ↓ 99ng/kg/min Unknown ↓ Discontinued	Hyperthyroidism 1 year and 5 months before administration: Administration of epoprostenol sodium was started due to pulmonary arterial hypertension. Day 1 of administration: Continuous intravenous administration of treprostinil was started for switching. Day 169 of administration: Hyperthyroidism occurred in the process of dose increase of treprostinil. There was no marked change of shortness of breath. Finger tremor was absent. Sweating was absent. BP 102/70mmHg, HR 93, thyroid stimulating hormone (TSH) 0.03 μIU/mL, free thyroxine (FT_4) 2.08 ng/dL. Day 196 of administration: Shortness of breath was exacerbated, with HR 100 and congestion on chest Xp. Day 201 of administration: As the symptoms of heart failure were further exacerbated, the patient was admitted to the hospital. The patient was negative for thyroid receptor antibody, Basedow disease, and thyroid stimulating antibody. But an increase in focal uptake was observed in RI testing, and the patient was diagnosed with hyperthyroidism due to nodular goiter. Treatment was started with potassium iodide 50 mg and thiamazole 15 mg. Day 203 of administration: (day of discontinuation) The dose of treprostinil was increased, but the response was inadequate, and therefore the drug was switched to epoprostenol sodium. 72 days after discontinuation:

				Hyperthyroidism recovering. BP104/50mmHg, HR76, TSH0.47μIU/mL, $FT_4$0.96ng/dL
	Concomitant medications: furosemide, spironolactone, riociguat, macitentan			

Laboratory Examination

Day of examination	Day 1 of administration	Day 134 of administration	Day 169 of administration	Day 201 of administration	2 days after discontinuation	72 days after discontinuation
FT_4 (ng/dL)	1.26	1.52	2.08	2.99	3.56	0.96
FT_3 (pg/mL)	3.97	-	-	8.16	6.78	-
TSH (μIU/mL)	0.41	0.66	0.03	< 0.01	< 0.01	0.47

2 Bosutinib

Brand name (name of company)	Bosulif Tablets 100 mg (Pfizer Japan Inc.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Chronic myelogenous leukemia with resistance or intolerance to prior drug therapies

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and erythema multiforme: TEN, oculomucocutaneous syndrome, and erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 2 years and 4 months (December 2014 to April 2017)
Cases related to TEN: 1 case (no fatal case)
Cases related to oculomucocutaneous syndrome: 4 cases (no fatal case)
Cases related to erythema multiforme: 4 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 600

Launched in Japan: December 2014

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Male 50s	Chronic myeloid leukemia (hypertension, type 2 diabetes mellitus)	500 mg for 14 days	TEN The patient had a history of allergy to nilotinib hydrochloride hydrate (hepatic dysfunction). Prior treatments for chronic myeloid leukemia: dasatinib hydrate, imatinib mesylate, nilotinib hydrochloride hydrate Day 1 of administration: Administration of bosutinib 500 mg/day was started. Day 8 of administration: Diarrhea (non-serious) occurred, but administration of this drug was continued. Day 11 of administration: Symptoms such as high fever (approx. 40°C), generalized rash (erythema), conjunctival hyperemia, and widespread stomatitis were observed, and then the patient was transported by ambulance. Skin symptoms at diagnosis: Conjunctival hyperemia, lip erosion, pharyngeal pain, genital erosion, systemic erythema and blistering and

				enanthema observed partially. Blisters occurred first and resulted in erosion. The symptoms occurred systemically, and blisters, erosion, epidermolysis, and erythema multiforme accounted for nearly 100% of the body surface area. Subjective symptoms: At first, pyrexia and pain occurred, and subsequently itching was observed. Conjunctival hyperemia and stomatitis in the whole mouth were observed. Staphylococcal scalded skin syndrome (SSSS) was ruled out. Skin biopsy was not performed. Based on the clinical course and physical findings, the patient was diagnosed with TEN (grade 4) associated with bosutinib. Administration of prednisolone 60 mg/day was started. The patient met the main findings as diagnostic criteria for TEN [(1) blisters, epidermolysis, and erosion accounting for more than 10% of the body surface area, (2) ruling out SSSS, and (3) pyrexia (≥38°C)], and therefore was definitely diagnosed with TEN (grade 4). Day 13 of administration: As heart failure was observed, administration of diuretics was started. After that, the clinical course was favorable. Day 14 of administration: (day of discontinuation) Administration of bosutinib was discontinued. 11 days after discontinuation: As the symptoms of TEN resolved, the patient was discharged from the hospital. Date unknown: Heart failure and diarrhea were recovering.
	Concomitant drugs: loperamide hydrochloride, betamethasone/d-chlorpheniramine maleate, peony root extract			
	Note(s) Company report			

Laboratory Examination

	12 days before administration	Day 11 of administration	Day 12 of administration	Day 14 of administration (day of discontinuation)	3 days after discontinuation	10 days after discontinuation
Body temperature (°C)	36.0	Approx. 40	39.6	-	37.0	36.5
WBC(cells/mm^3)	7800	-	13300	-	17100	9400
Eos (%)	4.0	-	3.0	-	2.5	5.0
Neu (%)	62.0	-	94.0	-	82.0	67.0
Baso (%)	0.0	-	0.0	-	0.0	1.0
Lym (%)	22.0	-	2.0	-	10.0	16.0
Mono (%)	12.0	-	1.0	-	5.5	11.0
Cr (mg/dL)	0.82	-	2.94	-	0.73	0.85
BUN (mg/dL)	14.5	-	39.4	-	10.4	23.4
ALT (IU/L)	74	-	75	-	110	204
AST (IU/L)	28	-	23	-	21	43
ALP (IU/L)	238	-	163	-	163	190
γ-GTP (IU/L)	84	-	52	-	77	82
Total bilirubin (mg/dL)	1.25	-	0.90	-	0.66	1.65
CRP(mg/dL)	0.28	-	14.51	-	2.16	0.15

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
2	Female 60s	Chronic myeloid leukemia (hypertension, asthma)	500 mg for 11 days	Stevens-Johnson syndrome The patient had a history of adverse reaction (skin eruption) to dasatinib hydrate and nilotinib hydrochloride hydrate. Prior treatments for chronic myeloid leukemia: Dasatinib hydrate and nilotinib hydrochloride hydrate Day 1 of administration: Administration of bosutinib 500 mg/day was started. Day 10 of administration: Skin eruption and pyrexia (39°C) occurred. Day 11 of administration: (day of discontinuation) The patient visited a skin clinic, and started administration of prednisolone 15 mg. Enanthema was observed with a histological picture consistent with drug eruption in skin biopsy, and therefore the patient was diagnosed with Stevens-Johnson syndrome. Administration of this bosutinib was discontinued. 2 days after discontinuation: As skin eruption tended to expand and fuse, the patient was admitted to the hospital. The dose of prednisolone was increased to 30 mg. Nature of skin eruption at hospital admission: Multiple red papules each measuring approx. several mm occurred, and they fused and expanded over the whole body. Rash was observed on the whole body including the trunk, limbs, head, and face. Rash was also observed in the mouth, but no abnormality was observed on the eyelids. Subjective symptoms at hospital admission: Itching, feeling hot, pharyngeal pain, and pyrexia. Blistering: None. 7 days after discontinuation: As redness decreased, the dose of prednisolone was reduced to 20 mg. 10 days after discontinuation: The dose of prednisolone was reduced to 10 mg. 13 days after discontinuation: Erythema improved, but pigmentation persisted. Although having recovered, the patient was diagnosed with having sequela.
	Concomitant drugs: amlodipine besilate, fluticasone propionate/formoterol fumarate hydrate			
	Note(s) Company report			

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
3	Female 60s	Chronic myeloid leukemia (diabetes, constipation)	200 mg for 4 days 300 mg for 6 days	Stevens-Johnson syndrome Day 1 of administration: Administration of bosutinib 200 mg/day was started. Day 5 of administration: The dose of bosutinib was increased to 300 mg/day. Day 9 of administration: At the time of doing rounds in the evening, small skin eruption was found on the upper parts of bilateral knees, and then the patient was put under follow-up observation. Day 10 of administration: (day of discontinuation) In addition to the upper parts of bilateral knees, skin eruption occurred on the prothorax. Olopatadine hydrochloride was orally administered, and topical hydrocortisone butyrate was administered. Administration of bosutinib was discontinued. 1 days after discontinuation: Skin eruption spread to the face, neck, arms, prothorax, back, and lower limbs. In the evening, lip swelling and enanthema in the mouth were observed. The nature of skin eruption is disseminated erythema tending to fuse, without blistering. The patient had subjective symptoms associated with pruritus. Pyrexia of 39.6°C was observed. The patient was diagnosed with Stevens-Johnson syndrome (grade 3), and intravenous infusion of prednisolone 50 mg was started. Skin symptoms at diagnosis: Conjunctival hyperemia (left), lip erosion (upper and lower), and erythema multiforme (5%-10% of the body surface area). 4 days after discontinuation: Skin eruption tended to improve. 6 days after discontinuation: The dose of prednisolone for intravenous infusion was reduced to 40 mg. 9 days after discontinuation: Intravenous infusion of prednisolone 40 mg was switched to oral administration of prednisolone 30 mg/day. 11 days after discontinuation: Skin eruption disappeared, and Stevens-Johnson syndrome resolved. 12 days after discontinuation: The dose of prednisolone for oral administration was reduced to 20 mg/day. 14 days after discontinuation: The dose of prednisolone for oral administration was reduced to 10 mg/day. 16 days after discontinuation: The dose of prednisolone for oral administration

				was reduced to 5 mg/day. 18 days after discontinuation: Oral administration of prednisolone was terminated. Date unknown: Skin biopsy was performed (Finding: superficial perivascular dermatitis with scleroderma).
	Concomitant medications: insulin aspart (genetical recombination), magnesium oxide			
	Note(s) Company report			

4

Revision of Precautions (No. 285)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs in accordance with the Notifications dated May 30, 2017

1 Cardiovascular agents-Miscellaneous

Treprostinil

Brand name	Treprost for Injections 20 mg, 50 mg, 100 mg, 200 mg (Mochida Pharmaceutical Co., Ltd)
Adverse reactions (clinically significant adverse reactions)	Hyperthyroidism: Hyperthyroidism may occur. Patients should be carefully monitored through a thyroid function test, etc. as necessary. If any abnormalities are observed, appropriate measures should be taken.

2 Hormones-Miscellaneous

Dulaglutide (genetical recombination)

Brand name	Trulicity Subcutaneous Injection 0.75 mg Ateos (Eli Lilly Japan K.K.)
Adverse reactions (clinically significant adverse reactions)	Anaphylaxis, angioedema: Anaphylaxis, or angioedema may occur. Patients should be carefully monitored. If any abnormalities including urticaria, lip swelling, pharyngeal/laryngeal oedema, and dyspnea are observed, administration of this drug should be discontinued and appropriate measures should be taken.

3 Antineoplastics-Miscellaneous

Bosutinib hydrate

Brand name	Bosulif Tablets 100 mg (Pfizer Japan Inc.)
Adverse reactions (clinically significant adverse reactions)	TEN, oculomucocutaneous syndrome (Stevens-Johnson syndrome), and erythema multiforme: TEN, oculomucocutaneous syndrome, and erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4

Biological preparations-Vaccines

Pneumococcal vaccine

Brand name	Pneumovax NP (MSD K.K.)
Adverse reactions (clinically significant adverse reactions)	Cellulitis/cellulitis-like reactions, injection site necrosis, injection site ulcer: After vaccination, cellulitis/cellulitis-like reactions (e.g., redness, swelling, pain, and pyrexia) may occur primarily on the injection site, resulting in necrosis or ulcer. If any of these conditions are observed, appropriate measures should be taken.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for 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 Adverse drug reaction (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 May 31, 2017)
◎: Products for which EPPV was initiated after April 1, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Aflibercept Beta (Genetical Recombination) Zaltrap 100 mg I.V. Infusion, 200 mg I.V. Infusion	Sanofi K.K.	May 29, 2017
◎	Guanfacine Hydrochloride Intuniv Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	May 26, 2017
◎	Forodesine Mundesine Capsule 100 mg	Mundipharma K.K.	May 24, 2017
◎	Ixazomib Citrate Ninlaro capsules 2.3 mg, 3 mg, 4 mg	Takeda Pharmaceutical Company Limited	May 24, 2017
◎	Ustekinumab (Genetical Recombination) *1 (1) Stelara Intravenous Infusion 130 mg, (2) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	May 24, 2017
◎	Drospirenone/Ethinylestradiol Betadex*2 YazFlex Combination Tablets	Bayer Yakuhin, Ltd.	April 21, 2017
	Golimumab (Genetical Recombination)*3 Simponi Subcutaneous Injection 50 mg, 100 mg Syringe	Janssen Pharmaceutical K.K.	March 30, 2017
	Zinc Acetate Dihydrate*4 Nobelzin Capsules 25 mg, 50 mg, Nobelzin Tablets 25 mg, 50 mg	Nobelpharma Co., Ltd.	March 24, 2017
	Omalizumab (Genetical Recombination)*5 Xolair for S.C. Injection 75 mg, 150 mg	Novartis Pharma K.K.	March 24, 2017
	Linaclotide Linzess Tablets 0.25 mg	Astellas Pharma Inc.	March 22, 2017
	Artemether/Lumefantrine Riamet Combination Tablets	Novartis Pharma K.K.	March 7, 2017
	Triamcinolone Acetonide MaQaid Intravitreal Injection 40 mg	Wakamoto Co., Ltd.	March 2, 2017
	Choriogonadotropin Alfa (Genetical Recombination) Ovidrel Syringe 250 μg	Merck Serono Co., Ltd.	March 1, 2017
	Apremilast	Celgene K.K.	March 1, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Otezla Tablets 10 mg, 20 mg, 30 mg		
	Dimethyl Fumarate Tecfidera Capsules 120 mg, 240 mg	Biogen Japan Ltd.	February 22, 2017
	Plerixafor Mozobil Subcutaneous Injection 24 mg	Sanofi K.K.	February 22, 2017
	Tenofovir Alafenamide Fumarate Vemlidy Tablets 25 mg	Gilead sciences K.K.	February 15, 2017
	Daclatasvir Hydrochloride / Asunaprevir / Beclabuvir Hydrochloride Ximency Combination Tablets	Bristol-Myers Squibb K.K.	February 15, 2017
	Etelcalcetide Hydrochloride Parsabiv Intravenous Injection for Dialysis 2.5 mg, 5 mg, 10 mg	ONO Pharmaceutical Co., Ltd.	February 15, 2017
	Pembrolizumab (Genetical Recombination) Keytruda Injection 20 mg, 100 mg*6	MSD K.K.	February 15, 2017
	Pembrolizumab (Genetical Recombination) Keytruda Injection 20 mg, 100 mg*7	MSD K.K.	February 15, 2017
	Ticagrelor Brilinta Tablets 60 mg, 90 mg	AstraZeneca K.K.	February 8, 2017
	EmtricitabineTenofovirAlafenamide 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*8	Novartis Pharma K.K.	December 19, 2016
	Eplerenone Selara Tablets 25, 50 mg*9	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*10	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

*1 (1) Induction therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments),
(2) maintenance therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments)

*2 Improvement of pain in endometriosis, dysmenorrhoea

*3 Improvement and maintenance for moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments)

*4 Hypozincemia

*5 Idiopathic chronic urticaria (limited to patients who are not adequately responsive to conventional treatments)

*6 PD-L1-positive, unresectable, advanced or relapsed non-small cell lung cancer

*7 Radically unresectable malignant melanoma

*8 Familial mediterranean fever, Tumour necrosis factor receptor-associated periodic syndrome, Mevalonate

kinase deficiency/Hyper IgD syndrome

*9 Chronic cardiac failure

*10 Improvement of pain in adenomyosis uteri