Pharmaceuticals and Medical Devices Safety Information

No. 333 May 2016

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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

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

Medi-navi is an email service that provides essential safety information released by the MHLW and PMDA. By registering, you can receive this information on the day of release.

Register here

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Pharmaceuticals and Medical Devices Safety Information
No. 333 May 2016
Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

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

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

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

Abbreviations

ADR	Adverse drug reaction
DLST	Drug lymphocyte stimulation test
DSU	Drug Safety Update
EPPV	Early Post-marketing Phase Vigilance
FPMAH	Federation of Pharmaceutical Manufactures' Associations of Japan
FY	Fiscal year
GAD	General Affairs Division
HPB	Health Policy Bureau
JCQHC	Japan Council for Quality Health Care
JPWA	Japan Pharmaceutical Wholesalers Associations
LI	Laser iridotomy
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MR	Medical representatives
MRI	Magnetic resonance imaging
MS	Marketing specialists
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PTP	Press Through Package
SD	Safety Division
SI	Stimulation index
SpO_2	Oxygen saturation
UBM	Ultrasound biomicroscopy

1

Use of “PMDA Medi-navi” and “My Drug List for Safety Updates”

Pharmaceuticals and Medical Devices Agency (PMDA) introduces the summary of improved functions for the safety information email alert service “PMDA Medi-navi” implemented in March 2016 to improve usability. Moreover, from early June, with a view to encourage further use of “PMDA Medi-navi”, registration forms for PMDA Medi-navi will be distributed to medical institutions, etc. (Refer to Figure 1) with the cooperation of the member companies of the Federation of Pharmaceutical Manufactures’ Associations of Japan (FPMAH) and Japan Pharmaceutical Wholesalers Associations (JPWA). Healthcare professionals may register to PMDA Medi-navi by sending the registration form via postcard or FAX. Healthcare professionals who have yet to register are encouraged to register.

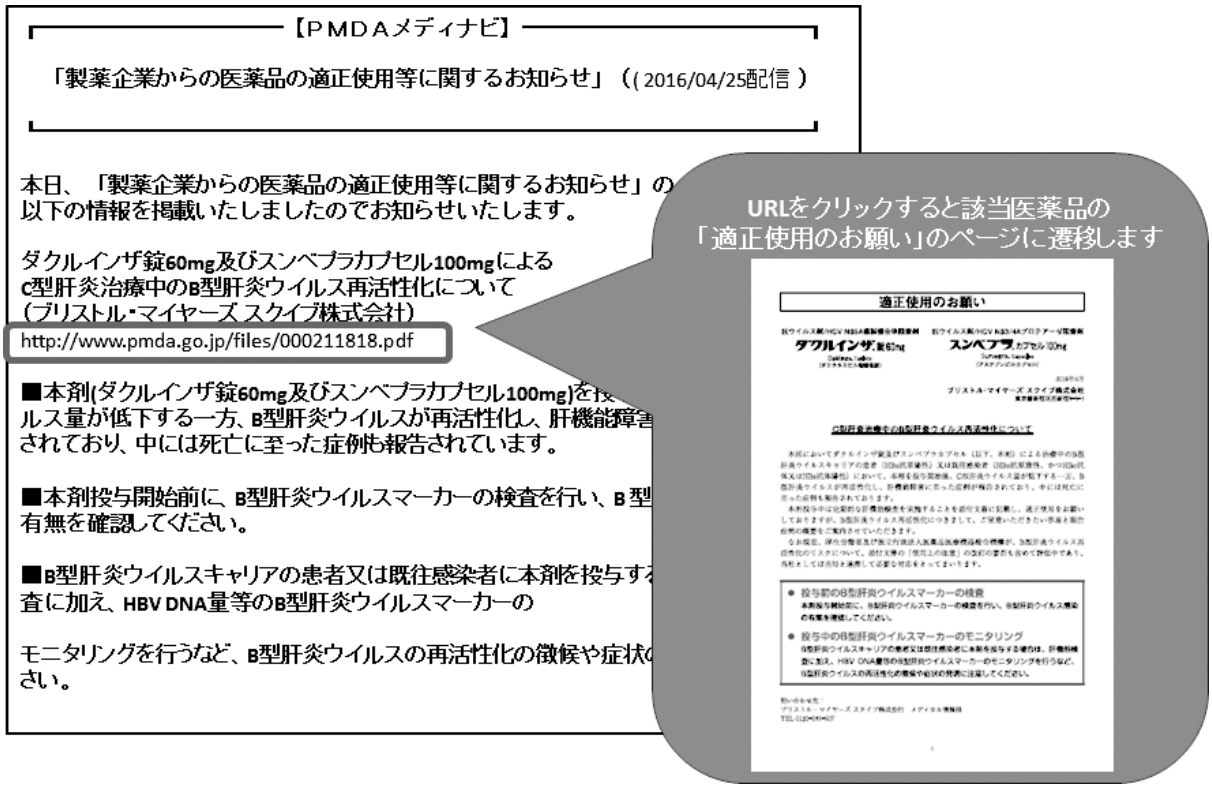
Figure 1. Registration form to be distributed by MR and MS

1. Introduction

The PMDA provides PMDA Medi-navi (Pharmaceuticals and Medical Devices Information Email Alert Service), a free service that sends email alerts when important information regarding safety of pharmaceuticals, medical devices, etc. are issued (Refer to Figure 2).

Ministry of Health, Labour and Welfare (MHLW) informs important safety information regarding pharmaceuticals, medical devices, etc. including “MHLW Urgent Safety Information” to healthcare professionals through PMDA Medi-navi. Furthermore, with the fiscal year (FY) 2016 modifications in the reimbursement of medical fees, registration to PMDA Medi-navi is now a requirement for calculating additional dispensing fees related to standard operations, indicating that PMDA Medi-navi is to be placed as an essential tool to gather information on pharmaceuticals.

Figure 2. Example of email sent through PMDA Medi-navi



2. Enhancement of functions provided through PMDA Medi-navi and My Drug List for Safety Updates

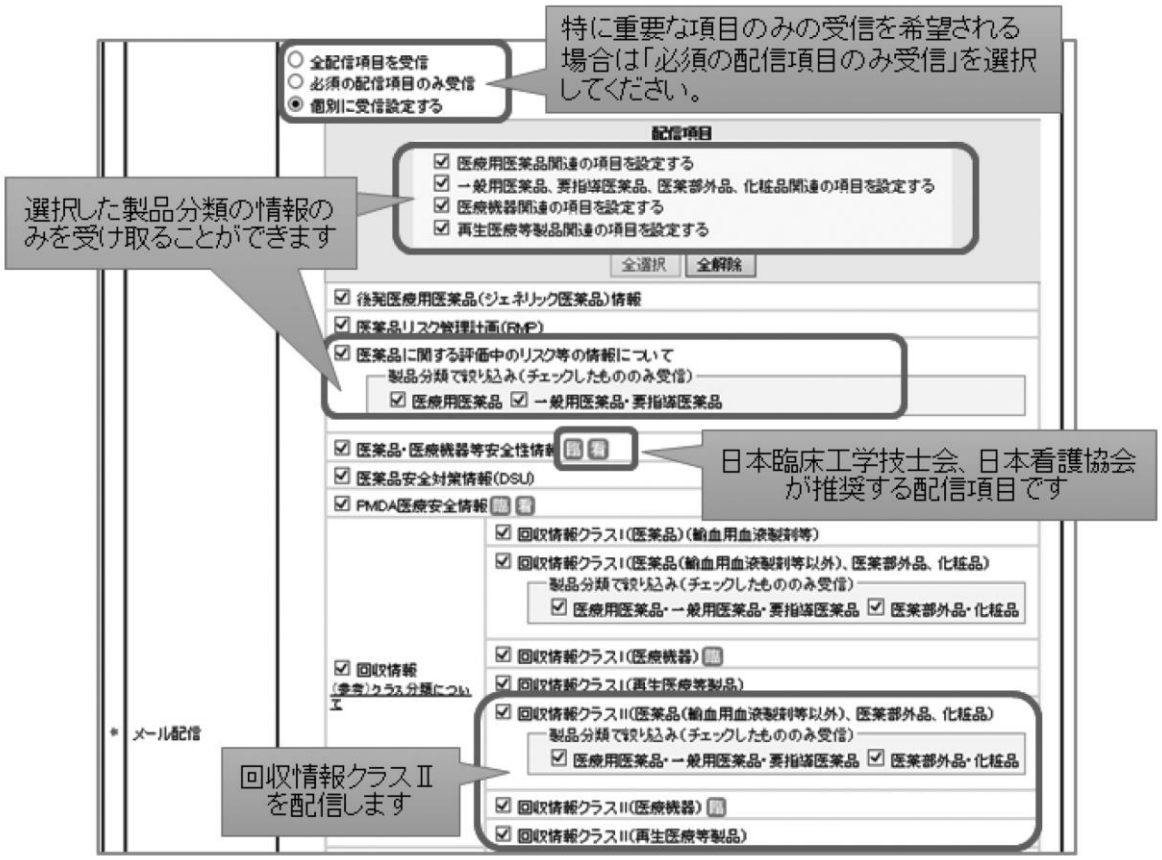
In the end of March 2016, PMDA enhanced functions of PMDA Medi-navi and its additional feature “My Drug List for Safety Updates” to improve usability. This section will introduce the new version of PMDA Medi-navi and “My Drug List for Safety Updates” which has become more user friendly.

<Major changes in functions of PMDA Medi-navi>

1. Emails can now be received in HTML format which is visually easier to understand. (To be started item by item)
2. Recall information (class II) on pharmaceuticals and medical devices is now available.
3. Screen for setting of information received has become more user friendly including below (Refer to Figure 3).
   - Information received can now be selected based on product category such as “items related to prescription drugs” or “items related to medical devices”.
   - Marks displayed next to items recommended by Japan Association for Clinical Engineers and Japanese Nursing Association, which makes selection of information received depending on occupation easier.
4. Registered email addresses can now be changed.
5. In addition to the above, particularly important information defined below is sent to all those registered on PMDA Medi-navi regardless of the setting of information received.
   - Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter)
   - Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter)

- MHLW notifications on revisions of Precautions
- MHLW notifications on self-check of medical devices
- Information on proper use of drugs
- Other important information (e.g. information regarding website maintenance, etc.)

Figure 3. Screen shot of improvements made in setting of information received



"My Drug List for Safety Updates" is an additional service that can be used by those registered on PMDA Medi-navi (Refer to Figure 4 and 5). With the registration of drugs, the most recent information including package insert information can be managed as a list in view format and utilized as an own drug list. For example, by exporting the list of codes for the National Health Insurance drug price list stored in receipt computer in CSV format followed by importing the list in "My Drug List for Safety Updates" using the retrieving feature, a drug list limited to the drugs handled in each medical institution can be created easily (Refer to Figure 6). A separate registration is required to use "My Drug List for Safety Updates" in addition to the registration of PMDA Medi-navi.

<Major additional function of "My Drug List for Safety Updates">

1. A function (*1) has been added where emails are sent to registered email addresses of those who request for such information when package insert information are renewed or when safety information is posted on PMDA website for registered drugs.
   - Risk management plan of drugs
   - Drug risk information of ongoing evaluation
   - MHLW pharmaceuticals and medical devices safety information (PMDSI) (*2)
   - Drug Safety Update (DSU) (*2)

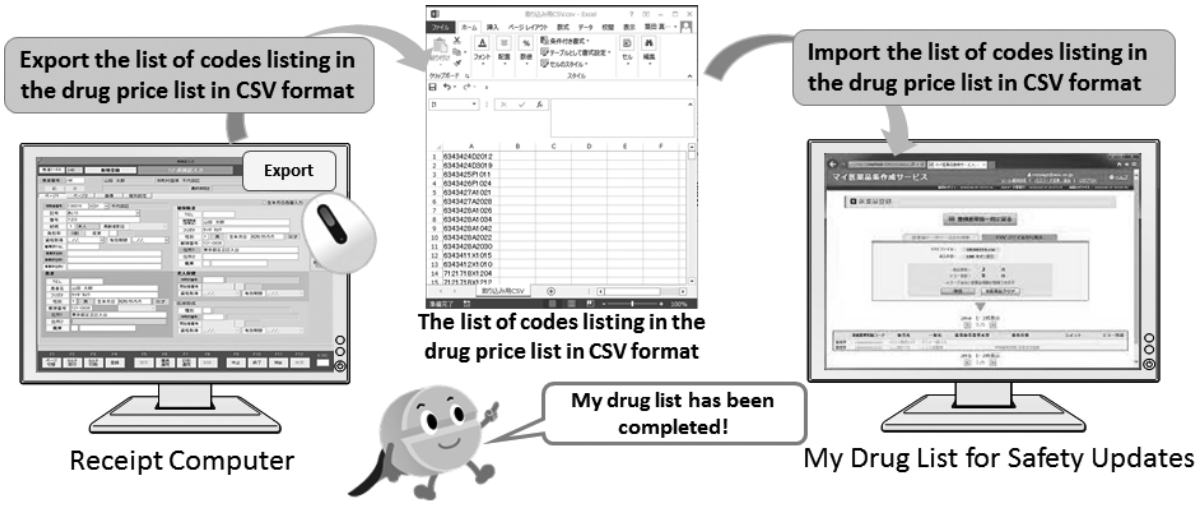
2. Modified portions of the package insert information of registered drugs can now be reviewed on the website through comparison between new and old package insert information.

*1: If the applicable information has already been received through PMDA Medi-navi, email alerts using this feature is not sent.
*2: In regards to PMDSI, emails are sent when brand names of the registered drugs are defined in “Important Safety Information” and “Revision of Precautions” section. In regards to DSU, emails are sent when brand names of the registered drugs are defined in “most important”, “important”, and “other” section.

Figure 4. Screen shot of “My Drug List for Safety Updates” (Registered drug list)

Figure 5. Screen shot of "My Drug List for Safety Updates" (Package insert information)

Figure 6. Example of how to create my drug list



3. Request for Use of "PMDA Medi-navi" as a Safety Measure

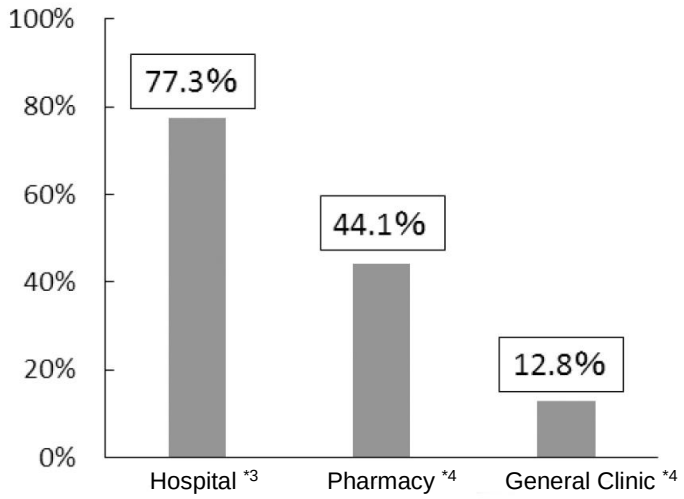
As of the end of March 2016, approximately 135 000 users have registered on PMDA Medi-navi. Based on the "Surveillance on Access to, Dissemination, and Utilization of Drug Safety Information in Medical Institutions" conducted by PMDA in FY 2014 and FY 2015, the percentage of institutions registered on PMDA Medi-navi is as follows: 77.3% among hospitals (*3), 12.8% among general clinics (*3), and 44.1% among pharmacies (*4), illustrating that the percentage of general clinics and pharmacies registered is lower compared to hospitals, and

PMDA Medi-navi is yet to be utilized well in general clinics and pharmacies (Refer to Figure 7).

PMDA Medi-navi is sent at the same time when safety information is issued, meaning that PMDA Medi-navi is an important tool for accessing important information promptly and reliably. Healthcare professionals are encouraged to refer to PMDA Medi-navi website (https://www.pmda.go.jp/safety/info-services/medi-navi/0007.html) (only available in the Japanese language) which introduces actual cases where PMDA Medi-navi is used in the medical field.

From early June, with the cooperation of FPMAH and JPWA, medical representatives (MR) and/or marketing specialists (MS) will begin distributing registration forms for PMDA Medi-navi to medical institutions, mainly general clinics and pharmacies (Refer to Figure 1, Page 3). Healthcare professionals may fill in the essential information in the registration form followed by sending it through an email or FAX. Registration on PMDA Medi-navi is easy, and healthcare professionals are encouraged to utilize the services to gather safety information on pharmaceuticals and medical devices, etc. in a prompt and comprehensive manner.

Figure 7. Registration status of PMDA Medi-navi for each institution type



*3: Percentage of institutions where the drug safety management supervisor or someone from the pharmacy department has registered to PMDA Medi-navi (FY 2014)
*4: Percentage of institutions where an individual's or representative's email address has been registered (FY 2015)

2

Precautions Concerning Recurrent and Similar Incidents of 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 Japan Council for Quality Health Care (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, 2015 and June 30, 2015, 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 "Mistakes in administration of potassium solutions" and "Mistakes in administration of antirheumatic methotrexate preparations".

2. Major Recurrent Incidents

(1) Mistakes in administration of potassium solutions

- Incident report

  Concentrated potassium solution was administered from the Y-site injection port using a syringe pump. (Fortunately, it was reported that this incident did not harm the patient.)

  The underlying cause included inconsistency in instructions regarding administration given by each individual physician and nurses' misunderstanding that concentrated potassium solution would be diluted if injected into the Y-site injection port since it will mix with the transfusion fluid in the main tube although nurses were aware that single shot intravenous injections of concentrated potassium solution was contraindicated.

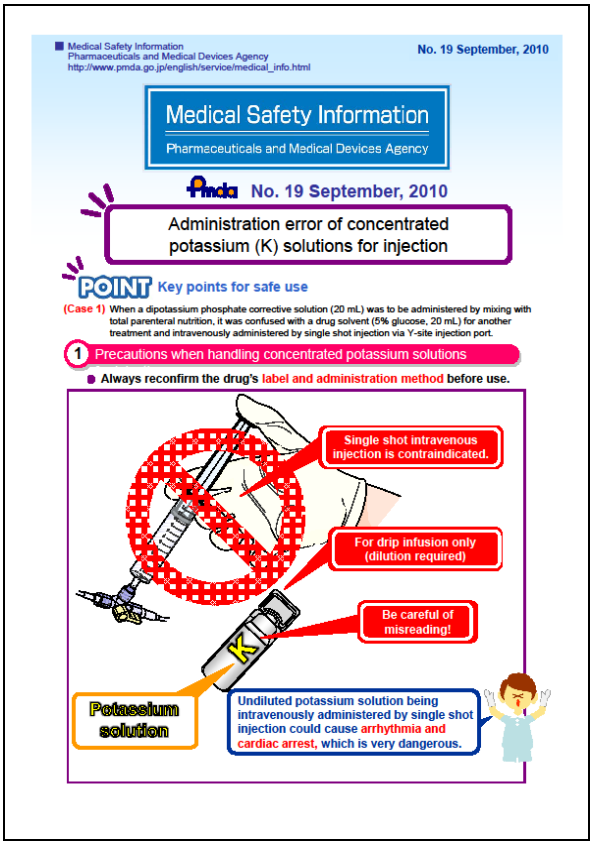
- Preventative measures for recurrence adopted by the facility where the incident occurred

  The facility distributed documents regarding precautions when using potassium solutions to each department in order to alert caution. In addition, the facility disseminated information related to precautions for diluted concentrations, etc. and consistency in administration instructions.

- Related notifications or precautions

  - Joint Notification of Health Policy Bureau (HPB) Notification No. 1204001 and Pharmaceutical and Food Safety Bureau (PFSB) / Safety Division (SD) No. 1204001 dated December 4, 2008
    "Reinforcement and Thorough Measures to Prevent Medical Accidents due to Similar Brand Names of Pharmaceuticals" (only available in the Japanese language)
    http://www.pmda.go.jp/files/000146020.pdf

➢ PMDA Medical Safety Information No. 19 “Administration error of concentrated potassium solutions for injection”
https://www.pmda.go.jp/files/000153903.pdf



Noted Incident 1

When a potassium phosphate, dibasic corrective solution (20 mL) was to be administered by mixing it with a high-calorie infusion, it was confused with a drug solvent (5% glucose, 20 mL) for another treatment and intravenously administered by a single shot injection via the Y-site injection port.

Preventative Measures for Recurrence

Always confirm the drug’s label and administration methods before use. In addition, there have been reports of mix-up due to wrong assumptions regarding the container shape, solution color, etc. It is important that the label is carefully confirmed or checked by more than one person.

Noted Incident 2

The instructions for potassium replacement indicated 2 ampoules of concentrated potassium solution with high-calorie infusion prior to administration. However, it was mistakenly administered by a single shot injection via the Y-site injection port of the patient route.

Preventative Measures for Recurrence

When potassium solutions are filled into the syringe and placed on a tray during preparation, there is a risk of mistaking administration methods.

In addition, the facility should consider switching to products with safeguards to prevent inadvertent administration ((1) products that are designed not to be connected to devices such as three-way stopcocks or injection needles, or (2) products that are designed that the drug solution cannot be injected even if it is connected to devices other than infusion bags).

(2) Mistakes in administration of antirheumatic methotrexate preparations

○ Incident report

A hospitalized patient took methotrexate preparations on consecutive days. As a result, the patient’s hepatic function declined and leukopenia was observed, and the patient required intensive care.

The underlying cause included lack of understanding among related personnel regarding administration method of this product as well as insufficient sharing of information regarding dosage and administration of drugs including those brought in by

the patient, and no utilization of the space provided on the package sheet to write down the dosing schedule.

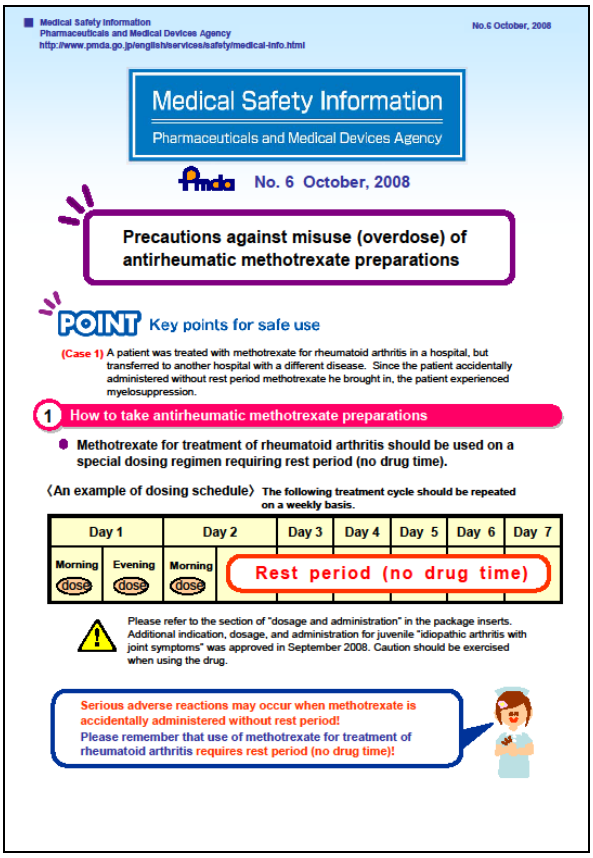
○ Preventative measures for recurrence adopted by the facility where the incident occurred

The facility sponsored a study meeting in regards to methotrexate preparations, and disseminated knowledge within the hospital of drugs requiring special dosing regimens such as those requiring rest periods (when the drug is not administered) as well as mentioned the need to write down the dosing schedule in the space provided on the package sheet.

In addition, instructions regarding drugs brought in by the patient were managed on a paper-basis; however, the hospital system was revised so that these drugs were displayed on the electronic medical charts similar to drugs prescribed in-hospital.

○ Related notifications or precautions

- PFSB/SD Notification No. 0829001 dated August 29, 2008
  "Measures to Prevent Medical Accidents Related to Misuse (Overdose) of Antirheumatic Methotrexate Preparations" (only available in the Japanese language)
  http://www.pmda.go.jp/files/000145608.pdf
  *The designs for packages of antirheumatic methotrexate preparations were revised so that the dosing schedule could be written after this notification was issued.
- Joint Notification of HPB Notification No. 1020001, PFSB/General Affairs Division (GAD) Notification No. 1020001, and PFSB/SD Notification No. 1020001 dated October 20, 2008
  "Handling of Antirheumatic Methotrexate Preparations in order to Prevent Misuse (Overdose)" (only available in the Japanese language)
  http://www.pmda.go.jp/files/000145447.pdf
- PMDA Medical Safety Information No. 6 "Precautions against misuse (overdose) of antirheumatic methotrexate preparations"
  https://www.pmda.go.jp/files/000153959.pdf



Noted Incident 1

A rheumatoid arthritis patient being treated with methotrexate was admitted to a different hospital for a different disease and accidentally administered on consecutive days without a rest period and thereby caused myelosuppression.

Preventative Measures for Recurrence

Need to make sure that understanding of oral drugs requiring special dosing regimens such as those requiring rest periods (when no drug is administered) is widespread.

Noted Incident 2

A rheumatoid arthritis patient brought in methotrexate preparations without indicating the dosing schedule in the space provided on the package. As a result, the methotrexate preparation was accidentally administered on consecutive days without a rest period and thereby caused leukopenia.

Preventative Measures for Recurrence

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.

Noted Incident 3

Because insufficient information was noted on the referral form when the patient was transferred to the other hospital, mistakes were made in the dosing and administration of the methotrexate preparation.

Preventative Measures for Recurrence

The drugs brought in by the patient on admission to the hospital should be carefully confirmed using a medication record book or referral form. If there are any queries regarding the drugs brought in by the patient, the prescribing physician should be consulted. In addition, prescriptions or referral forms should clearly include details related to time, date, and number of dosing.

(3) Other recurrent and similar incidents

(Analysis results of cases reported to the JCQHC between January 1 and June 30, 2015)
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	Prescription error of the total weight of the formula and weight of the active ingredient of powder	The method of the describing details of powders on the prescription is basically described as the weight of the formula contents, and drug name is described as the brand name, and, if the weight of the drug substance was exceptionally described, clearly show that it is the [amount of drug substance]. Joint Notification of HPB No. 0129-3 and PFSB Notification No. 0129-5 dated January 29, 2010 "Publication of the Expert Panel Report on Description Method of Oral Prescription Drugs (request for dissemination)" (Only available in the Japanese language) http://www.pmda.go.jp/files/000145210.pdf
2	Accidental 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)" (Only available in the Japanese language) http://www.pmda.go.jp/files/000415758.pdf
3	Error in dosage unit of insulin administered	When preparing insulin, confirm that there are no errors in unit conversion (i.e. number of mL). (1mL of insulin injection fluid is 100 units) Be cautious about mix-ups between insulin syringes and other syringes. PMDA Medical Safety Information No. 23 "Precautions in Handling of Insulin Syringes" http://www.pmda.go.jp/files/000153172.pdf
4	Use of expired vaccines	Pay attention to the expiration dates of vaccine products in stock regularly. PMDA Medical Safety Information No. 40 "Precautions in Handling of Vaccines" http://www.pmda.go.jp/files/000153533.pdf

[Medical Devices]

No.	Content	Preventative Measures for Recurrence and Related Notifications
1	Metal materials pulled with great force by MRI machines	Make sure that there are no magnetic objects before entering the magnetic resonance imaging (MRI) room. (The MRI room has a strong magnetic field at all times, and it is strictly prohibited to bring magnetic objects into the MRI room.) PMDA Medical Safety Information No. 26 "Precautions for MRI Scans (Part 2)" http://www.pmda.go.jp/files/000153828.pdf
2	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
3	Incorrect intubation of nasogastric tubes	After tube 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
4	Subcutaneous catheter fracture due to long-term use and physical stress	Be cautious about fractures, etc. associated with long-term use. In addition, if a subcutaneous catheter is placed in the subclavian vein, make sure that the catheter is not pinched between the first rib and the clavicle. PFSB/SD Notification No. 0525-1 and PFSB/Evaluation and Licensing Division/Office of Medical Devices Evaluation Notification No. 0525-1 dated May 25, 2011 "Revisions of Package Inserts Related to Subcutaneous Ports and Catheters" (only available in the Japanese language) http://www.pmda.go.jp/files/000148739.pdf *PMDSI No. 281 Review Commentary https://www.pmda.go.jp/files/000153536.pdf#page=5

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 family, 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.

(Reference)

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

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

3. PMDA Medical Safety Information
   https://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 April 21, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Sodium chloride/potassium chloride/sodium sulfate anhydrous/ Macrogol 4000/Ascorbic acid/sodium L-ascorbate

Brand name (name of company)	Moviprep Combination Oral Solution (EA Pharma Co., Ltd.)
Therapeutic category	Miscellaneous non-main therapeutic purpose agents
Indications	Elimination of intestinal contents as pretreatment prior to colonoscopy or large intestine surgery

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Syncope and loss of consciousness: Syncope and loss of consciousness may occur, and there have been reports of cases associated with decreased blood pressure. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be adopted.
For home use, patients should be instructed with reference to "Important Precautions" section.

Reference information

The number of reported adverse reactions (for which a causal relationship to the product could not be ruled out) for the past 2 years and 9 months (from June 2013 to February 2016).
Cases associated with syncope and loss of consciousness: 6 cases (no fatal case)
The number of patients using this drug estimated by the marketing authorization holder (MAH):
Approximately 1 650 000 (from January 2015 to December 2015)
Launched in Japan:
June 2013

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Colonoscopy (cardiac valve disease, hypertension, arrhythmia)	1 L for 1 day	**Loss of consciousness** 1 day before administration: The patient was orally being administered sodium picosulfate hydrate but did not respond. There was no bowel movement. Day 1 of administration: The patient had a final bowel movement in the morning after orally administering sodium picosulfate hydrate. 1L of this drug was administered. There was bowel movement during administration. After administration of 1L of this drug, the patient suffered from loss of consciousness. Carotid artery was non-palpable. The patient had coldness in the limbs. It was not possible to measure blood pressure.

				The patient was transferred to the ER using a stretcher. 15 minutes after loss of consciousness, administration of 500 mL initiating solution was initiated. Blood pressure was 42/30 mmHg, and heart rate was about 40 times/minute. 3 minutes after initiating administration of initiating solution, blood pressure was 72/40 mmHg, and heart rate was about 40 times/minute. Atropine sulfate hydrate 0.5 mg was administered. 16 minutes after administering atropine sulfate hydrate, blood pressure was 97/51 mmHg, heart rate was about 70 times/minute, and consciousness level was recovered. The patient was placed under observation. 4 hours and 7 minutes after administering atropine sulfate hydrate, blood pressure was 112/59 mmHg, and heart rate 64 times/minute. The patient cancelled the colonoscopy and went home.
	Concomitant medications: carvedilol, telmisartan, omeprazole, verapamil hydrochloride			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Colonoscopy (hypertension, rheumatic disorder)	1.2 L for 1 day	**Loss of consciousness** Day 1 of administration: The patient visited the hospital for a colonoscopy. The patient had a bowel movement while being administered 1.2 L of this drug and 0.6 L of water. The patient suffered from loss of consciousness after bowel movement and the patient was unable to breathe spontaneously. 1 minute after loss of consciousness, the patient vomited and spontaneous breathing resolved. Blood pressure was 118/56 mmHg, Oxygen saturation (SpO_2) was 98%. Heart rate was 54 times/minute, and consciousness was clear. 3 minutes after loss of consciousness, administration of 500 L maltose-lactated Ringer's solution was initiated. The patient was transferred to the treatment room using a wheelchair. (The patient did not have any symptoms such as nausea and light-headedness while being transferred). 15 minutes after loss of consciousness, blood pressure was 110/68 mmHg, SpO_2 was 95%, and heart rate was 60 times/minute. Consciousness was clear. The patient was placed under observation. 45 minutes after loss of consciousness, while a slight light-headedness remained, the patient was able to respond without any problems to the physician's questions. 90 minutes after loss of consciousness, the patient was able to go to the toilet while being accompanied by a nurse. (Blood pressure was 120/58 mmHg and heart rate was 72 times/minute). 95 minutes after loss of consciousness, the patient was instructed to rest at home and consume liquid, and was sent home after being accompanied by family members.
	Concomitant medications: none			

2 a. Vildagliptin
b. Vildagliptin/Metformin hydrochloride
c. Sitagliptin phosphate hydrate

Brand name (name of company)	a. Equa Tablets 50 mg (Novartis Pharma K.K.) b. Equmet Combination Tablets LD and HD (Novartis Pharma K.K.) c. Glactiv Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (Ono Pharmaceutical Co., Ltd.) d. Januvia Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (MSD K.K.)
Therapeutic category	Antidiabetic agents
Indications	a ,c-d Type 2 diabetes mellitus b. Type 2 diabetes mellitus Only for which treatment with concomitant vildagliptin and metformin hydrochloride is judged to be appropriate

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Pemphigoid: Pemphigoid may occur. If blister, erosion, or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures such as discontinuation of administration should be adopted.

Reference information

The number of reported adverse reactions (for which a causal relationship to the product could not be ruled out) for the past 2 years and 11 months (from April 2013 to March 2016).

Cases associated with pemphigoid:
a. 8 cases (no fatal case)
b. No case reported
c. 3 cases (no fatal case)

The number of patients using this drug estimated by the MAH:
a. Approximately 1 110 000 (from January 2015 to December 2015)
b. Approximately 8 000 (from launch to December 2015)
c. Approximately 2 180 000 (from August 2014 to August 2015)

Launched in Japan:
a. April 2010
b. November 2015
c. 12.5 mg Tablets: November 2013
25 mg, 50 mg, and 100 mg Tablets: December 2009

Case summary (Sitagliptin phosphate hydrate)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Diabetes mellitus (chronic pigmented purpura)	25 mg for 9 months	**Bullous pemphigoid** Day 1 of administration: Treatment was initiated with this drug. Month 3 of administration: A blister appeared on the right anterior chest, but it spontaneously ruptured and was resolving naturally. Month 4 of administration: A blister associated with pruritus and pain appeared on the left abdomen, but this was also resolving naturally. Month 7 of administration: Multiple minor erythema and blisters appeared on the trunk of the body. Blisters spread and covered the entire body after aggravation. Month 8 of administration: The patient consulted a clinic. Treatment with oral drugs + topical drugs (bepotastine besilate tablets, syofusan powder, betamethasone butyrate propionate ointment,

				heparinoid ointment) was administered but conditions did not resolve. Month 8 of administration: The patient consulted a hospital dermatologist. The patient tested negative for anti-desmoglein antibodies (<3.0 U/mL). The patient was diagnosed with bullous pemphigoid as he tested strongly positive for anti-BP (bullous pemphigoid) 180 antibodies (356 U/mL) and based on the pathological results, and was admitted to the hospital for treatment. Treatment with prednisolone 40 mg and diflorasone diacetate topical ointment was initiated. Date unknown: Drug lymphocyte stimulation test (DLST) yielded a positive result for this drug but patch test yielded a negative result. Month 8 of administration: Decreased dose of prednisolone to 30 mg. Month 9 of administration: The patient was discharged from the hospital temporarily as symptoms was resolving. Date unknown: Blisters appeared on the head, face, and neck as well. Month 9 of administration: Confirmed exacerbation of blister formation again on an outpatient basis, and admitted the patient to the hospital again. Anti-BP180 antibodies was ≧1000 U/mL. Dosage of prednisolone was increased to 50 mg but conditions did not resolve. Month 9 of administration: Plasma exchange therapy was conducted (3 times). Month 9 of administration (Day of discontinuation): Drug-induced bullous pemphigoid was suspected due to this drug; therefore, administration with this drug was discontinued. Date unknown: Prednisolone and cyclosporine was administered concomitantly and symptoms remitted. 3 days after discontinuation: Symptoms seemed to be resolving, and dosage of prednisolone was decreased to 40 mg. 8 days after discontinuation: Dosage of prednisolone was decreased to 35 mg. 11 days after discontinuation: The patient was discharged from the hospital. Bullous pemphigoid was resolved.
	Concomitant medications: betamethasone butyrate propionate, levocetirizine hydrochloride, ascorbic acid/calcium pantothenate, heparinoid			

3 Fexofenadine hydrochloride/pseudoephedrine hydrochloride

Brand name (name of company)	Dellegra Combination Tablets (Sanofi K.K.)
Therapeutic category	Miscellaneous allergic agents
Indications	Allergic rhinitis

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Acute generalised exanthematous pustulosis: Acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored. If symptoms, such as pyrexia, erythema, and many small pustules, are observed administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference information

The number of reported adverse reactions (for which a causal relationship to the product could not be ruled out) for the past 2 years and 10 months (from April 2013 to February 2016).
Cases of acute generalised exanthematous pustulosis: 1 case (no fatal case)
The number of patients using this drug estimated by the MAH:
Approximately 1 340 000 (2015)
Launched in Japan:
February 2013

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Allergic rhinitis (allergic rhinitis, upper respiratory tract infection)	Fexofenadine hydrochloride 120 mg/ pseudoephedrine hydrochloride 240 mg for 3 days ↓ No administration for 10 days ↓ Fexofenadine hydrochloride 120 mg/ pseudoephedrine hydrochloride 240 mg for 3 days	**Acute generalised exanthematous pustulosis:** Day 1 of administration: This drug and levocetirizine hydrochloride (administered until 1 day after administration of this drug) was prescribed for the treatment of allergic rhinitis. Garenoxacin mesilate hydrate and ambroxol hydrochloride (administered until Day 5 of administration of this drug) was prescribed for the treatment of acute upper respiratory tract inflammation. Day 3 of administration: The patient suffered from pyrexia and erythema appeared on the entire body. The patient consulted a nearby clinic. Administration of this drug was discontinued. Cefcapene pivoxil hydrochloride hydrate, betamethasone *d*-chlorpheniramine maleate, and steroid ointment was prescribed. Symptoms was resolving. Day 14 of administration: Oral administration of this drug was re-initiated. Day 16 of administration (Day of discontinuation): The patient suffered from pyrexia and erythema appeared on the entire body. The patient consulted a nearby clinic. Administration of this drug was discontinued. Cefditoren pivoxil, levocetirizine hydrochloride, and betamethasone *d*-chlorpheniramine maleate was prescribed but conditions did not resolve. 1 day after discontinuation: The patient was referred to a dermatologist. The patient

				suffered from pyrexia at 38°C. Erythema with strong redness was observed all over the body, and there was erythema associated with abscess as well. The patient was admitted to the hospital the same day. 2 days after discontinuation: Oral administration of prednisolone 20 mg/day. Pyrexia resolved promptly and rash was resolving as well. Dermatological histopathology Blister portion: Partial parakeratosis, with subcorneal neutrophil abscess, with epidermal cell oedema and subepidermal blisters, and with surface epidermal oedema and neutrophils within continuous blisters. Neutrophil tissue infiltration was observed in dermal blood vessels and peripheral diffuse epidermis. Nuclear formation of endothelial swelling stood out as well. Single cell necrosis is scarce. Erythema portion with strong redness: Mild surface epidermal oedema and blisters. Similar form to erythema multiforme. Not particularly inconsistent with drug eruption. 6 days after discontinuation: The patient was discharged from the hospital. 13 days after discontinuation: Rash was resolving and almost none were observed. 41 days after discontinuation: Patch test Fexofenadine hydrochloride (1%, 10%, 30%) 48 hr (-), 72 hr (-) This drug (1%, 10%, 30%) 48 hr (+), 72 hr (+) DLST Fexofenadine hydrochloride S.I. 107% (-) This drug S.I. 180% (-)
	Concomitant medications: levocetirizine hydrochloride, garenoxacin mesilate hydrate, ambroxol hydrochloride			

4 Peramivir hydrate

Brand name (name of company)	Rapiacta Bag for Intravenous Drip Infusion 300 mg, Rapiacta Vial for Intravenous Drip Infusion 150 mg (Shionogi & Co., Ltd.)
Therapeutic category	Antivirals
Indications	Type A or B influenza virus infection

PRECAUTIONS (underlined parts are revised)

Important Precautions

Shock and anaphylaxis may occur. During the administration patients should be carefully monitored under the conditions where emergency treatment is available. Shock and anaphylaxis may occur even after discontinuation of administration, and, therefore, caution should be exercised.

Adverse reactions (clinically significant adverse reactions)

Shock and anaphylaxis: Shock and anaphylaxis (decreased blood pressure, facial pallor, cold sweat, dyspnoea, urticaria, etc.) 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.

Reference information

The number of reported adverse reactions (for which a causal relationship to the product could not be ruled out) for the past 2 years and 10 months (from April 2013 to February 2016).
Cases associated with anaphylaxis: 8 cases (1 fatal case)
The number of patients using this drug estimated by the MAH:
Approximately 170 000 (from February 2015 to January 2016)
Launched in Japan:
January 2010

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Less than 10 years old	Influenza (asthma)	200 mg 1 administration	The patient did not have any other medical history. Day 1 of administration: SpO_2 was approximately 80%, and the patient consulted the hospital with breathing difficulty as his main complaint. Inhaled short-acting beta-2 agonist and intravenously administered prednisolone sodium succinate 1.5 mg/kg for the treatment of severe bronchial asthma attack. Respiratory conditions stabilized and SpO_2 levels were maintained through inhalation of oxygen 5 L/minute. 200 mg of this drug (10 mg/kg) was administered as an intravenous drip over 30 minutes for the treatment of influenza infection (Type A+, body temperature 40°C). 10 minutes after administration: Carbocisteine, ambroxol hydrochloride, and butyric acid bacteria (C. butyricum Miyairi) formulation was administered orally. 1 hour and 40 minutes after administration: The patient pressed the nurse call due to breathing difficulties and systemic pruritus. Systemic welts were found mainly around the trunk of the body. 1 hour and 50 minutes after administration: The patient was diagnosed with anaphylaxis (no decrease in blood pressure). Symptoms was resolving quickly after adrenaline 0.01 mg/kg was administered intravenously.

				Famotidine and *d*-chlorpheniramine maleate was administered. 5 hours and 40 minutes after administration: Prednisolone succinate 0.5 mg/kg was administered intravenously. Carbocisteine, ambroxol hydrochloride, and butyric acid bacteria (C. butyricum Miyairi) formulation was administered orally. 6 hours and 40 minutes after administration: Urticaria observed again. No respiratory symptoms, and no decrease in blood pressure. Olopatadine hydrochloride was orally administered and symptoms seem to be resolving. Steroids were switched to betamethasone sodium phosphate injection while the patient was hospitalized. 1 day after administration: The patient was resolving.
	Concomitant medications: prednisolone sodium succinate, carbocisteine, ambroxol hydrochloride, butyric acid bacteria (C. butyricum Miyairi) formulation			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Influenza (hypertension, type 2 diabetes mellitus, chronic hepatitis)	300 mg 1 administration	The patient did not have any other medical history. Day 1 of administration: The patient visited the hospital for pyrexia, pharynx pain. Influenza test was positive (++). The patient was diagnosed with Influenza A virus infection and acute pharyngitis. 300 mg/60mL of this drug was administered as an intravenous drip. IV drip infusion of cefazolin sodium hydrate 2.0g + physiological saline 250 mL was started. 15 minutes after administration: The patient developed dyspnea, drop in blood pressure (systolic blood pressure 50mmHg), disturbed consciousness immediately before the end of infusion. The patient was diagnosed with acute circulatory failure. Oxygen therapy and fluid replacement were started. 45 minutes after administration: After oxygen therapy and fluid replacement, level of consciousness was slightly recovering. The patient was transported by the ambulance to the hospital and admitted. The patient recovered after administration of vasopressor (adrenaline) and steroids. 6 day after administration: The patient was discharged from the hospital.
	Concomitant medications: cefazolin sodium hydrate, irbesartan, amlodipine besylate salt formulation, glimepiride, Sitagliptin phosphate hydrate, ursodeoxycholic acid			

5 a,b Levodopa
c~e. Levodopa/Benserazide hydrochloride
f,g Levodopa/Carbidopa hydrate
h. Levodopa/Carbidopa hydrate/Entacapone

Brand name (name of company)	a. Dopasol Tablets 200 mg (Daiichi Sankyo Co., Ltd.) b. Dopaston Capsules 250 mg, Dopaston Powder 98.5%, Dopaston Intravenous Injections 25 mg and 50 mg (Ohara Pharmaceutical Co., Ltd.) c. Neodopasol Combination Tablets (Daiichi Sankyo Co., Ltd.) d. Madopar Combination Tablets (Chugai Pharmaceutical Co., Ltd.) e. EC-Doparl Combination Tablets (Kyowa Hakko Kirin Co., Ltd.) f. Neodopaston Combination Tablets L100 and L250 (Daiichi Sankyo Co., Ltd.), and the others g. Menesit Combination Tablets 100 and 250 (MSD K.K.), and the others h. Stalevo Combination Tablets L50 and L100 (Novartis Pharma K.K.)
Therapeutic category	Antiparkinsonian agents
Indications	a. Treatment and prophylaxis of the following symptoms associated with Parkinson's disease/Parkinson's syndrome Akinesia, muscle rigidity, tremor, impaired activities of daily living, mask-like faces, gait disturbance, language disorder, abnormal posture, pulsion, oily face, dysgraphia, psychiatric symptom, and ptyalism b-g. Parkinson's disease and Parkinson's syndrome h. Parkinson's disease (when circadian rhythm of symptoms [wearing-off] is observed in administration of levodopa/carbidopa)

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reaction)

Angle closure glaucoma: Angle closure glaucoma associated with sudden increased intraocular pressure may occur. If any abnormalities, such as blurred vision, eye pain, hyperemia, headache, and nausea, are observed, administration of this drug should be discontinued, and appropriate measures should be adopted immediately.

Reference information

The number of reported adverse reactions (for which a causal relationship to the product could not be ruled out) for the past 2 years and 10 months (from April 2013 to February 2016).

Cases associated with angle closure glaucoma:
a and b. No case reported
c to e. 2 cases (no fatal case)
f and g. No case reported
h. No case reported

The number of patients using this drug estimated by the MAH:
a. Approximately 200 (from January 2015 to December 2015)
b. Approximately 10 000 (from January 2015 to December 2015)
c. Approximately 5 000 (from January 2015 to December 2015)
d. Approximately 80 000 (from June 2013 to June 2014)
e. Approximately 35 000 (from October 2014 to September 2015)
f. Approximately 23 000 (from January 2015 to December 2015)
g. Approximately 90 000 (FY 2015)
h. Approximately 9 000 (from January 2014 to December 2014)

Launched in Japan:
a and b. January 1972
c to g. February 1980

h. 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 80s	Parkinson's disease (Postoperative prostate cancer, chronic kidney disease, emphysema, psoriasis vulgaris)	Unknown	**Bilateral acute angle closure glaucoma** History of administration with this drug is unknown. 2 days before administration: The patient bruised his entire body due to a fall. Day 1 of administration: Consulted a nearby internist 2 days after being injured. The patient was diagnosed with acute aggravation of chronic kidney disease and with Parkinson's disease, and was therefore prescribed this drug as well as pramipexole hydrochloride hydrate. Day 2 of administration: Hallucinations were confirmed after oral administration; therefore, administration of pramipexole hydrochloride hydrate was discontinued. Day 4 of administration: The patient's weight decreased by 10 kg, and the patient complained of frontal headache, nausea, and blurred vision in the early morning and was unable to stand; therefore, the patient was transported by the ambulance to the hospital. When the patient was asked during the first consultation about the oral medication he took, he mentioned taking 15 drugs, of which 3 were drugs with anticholinergic effects. Laboratory findings during first consultation: Visual acuity: Right eye 0.4 (0.5×S+3.00D=C-2.25D Ax 90°) Left eye 0.2 (0.4×S+1.75D=C-1.50D Ax 80°) Intraocular pressure: Right eye 47 mmHg, Left eye 48 mmHg Pupil diameter: Perfectly round and 2.2 mm for both eyes There was no inflammation in the anterior chamber, and, although the patient had conjunctival hyperaemia, there was no apparent corneal oedema. Peripheral anterior chamber depth was Grade 1 narrow-angle glaucoma on the van Henrick Method, and gonioscopy indicated Grade I on the Shaffer classification. Mild nuclear cataract was observed in both eyes, and axial length was 23.95 mm for the right eye and 23.94 mm for the left eye. There was no papilloedema or vasculitis seen on the ocular fundus, and there was no choroidal haemorrhage either. Ultrasound biomicroscopy (UBM) conducted in the dark room indicated ciliochoroidal effusion throughout the entire circumference. While lordosis of the iris was mild, the corner angle demonstrated functional obstruction. In addition, there were no findings to suggest lens subluxation. Day 5 of administration: Onset of acute angle closure glaucoma. Suspecting that the patient was suffering from acute angle closure glaucoma, frequent ophthalmic solution of 2% pilocarpine hydrochloride, 1% brinzolamide, and 0.1% betamethasone sodium phosphate was initiated after UBM. However, ocular pressure only decreased to 43 mmHg in both eyes. Optical coherence tomography of the anterior ocular segment after ocular instillation of pilocarpine hydrochloride indicated that anterior chamber depth was 1.495 mm for the right eye and 1.522 mm for the left eye,

				which is shallow, and the temporal corner angle demonstrated functional obstruction. The patient had emphysema; therefore, beta-blocker ophthalmic solutions could not be administered. In addition, oral carbonic anhydrase inhibitor and drip infusion of hyperosmotic agents could not be administered as the patient had renal impairment. In order to exclude angle closure mechanisms due to pupillary block, laser iridotomy (LI) was conducted. Ophthalmic solutions of 1% apraclonidine hydrochloride was administered before and after LI. Ocular pressure in both eyes decreased to 20 mmHg after LI. Ophthalmic solution of pilocarpine hydrochloride was only used before L1, after which administration was discontinued. Dexamethasone sodium phosphate was administered as subconjunctival injections in both eyes after LI. Administration of brinzolamide ophthalmic solution 2 times/day and betamethasone sodium phosphate ophthalmic solution 3 times/day was continued in both eyes while being cautious of renal impairment. Day 6 of administration: Anterior chamber depth further narrowed compared to first consultation, and anterior chamber depth was 1.199 mm for the right eye and 1.097 mm for the left eye. Ocular pressure was 20 mmHg for the right eye and 21 mmHg for the left eye. Day 10 of administration: Ocular pressure was 13 mmHg for the right eye and 12 mmHg for the left eye. Anterior chamber depth deepened to 2.185 mm for the right eye and 2.345 mm for the left eye. Day 20 of administration: Anterior chamber depth further deepened to 2.421 mm for the right eye and 2.478 mm for the left eye indicating that corner angle dilated. Anterior chamber depth increased by approximately 1 mm compared to first consultation on the same day. UBM conducted on this day demonstrated that ciliochoroidal effusion of the entire circumference observed during first consultation completely disappeared and corner angle dilated. Corrected visual acuity of both eyes resolved until 0.9, and ocular pressure 12 mmHg for the right eye and 15 mmHg for the left eye without ophthalmic solutions of glaucoma agent. Gonioscopy indicated Grade IV on the Shaffer classification, and corner angle was completely open. Approximately Month 1 of administration (Day of discontinuation): Treatment with this drug was completed.
	Concomitant medications: pramipexole hydrochloride hydrate			

4

Revision of Precautions (No. 274)

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 April 21, 2016.

1

Antiepileptics

Gabapentin

Brand name	Gabapen Tablets 200 mg, 300 mg, and 400 mg, Gabapen Syrup 5% (Pfizer Japan Inc.)
Adverse reaction (clinically significant adverse reaction)	**Anaphylaxis**: Anaphylaxis (angioedema, dyspnoea, etc.) 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

Miscellaneous central nervous system agents

Gabapentinenacarbil

Brand name	Regnite Tablets 300 mg (Astellas Pharma Inc.)
Adverse reaction (clinically significant adverse reaction)	**Anaphylaxis**: Anaphylaxis (angioedema, dyspnoea, etc.) 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.

3

Anticoagulants

Edoxaban tosilate hydrate

Brand name	Lixiana Tablets 15 mg, 30 mg, and 60 mg (Daiichi Sankyo Co., Ltd.)
Adverse reaction (clinically significant adverse reaction)	**Hepatic function disorder and jaundice**: Hepatic function disorder or jaundice associated with increased levels of aspartate aminotransferase (glutamate oxaloacetate transaminase), alanine aminotransferase (glutamate pyruvate transaminase), etc. 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.

4 **Anticoagulants**

Rivaroxaban

Brand name	Xarelto Tablets 10 mg and 15 mg, Xarelto Fine Granules 10 mg and 15 mg (Bayer Yakuhin, Ltd.)
Adverse reaction (clinically significant adverse reaction)	**Thrombocytopenia**: Thrombocytopenia 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.

5 **Miscellaneous antineoplastics**

Afatinib maleate

Brand name	Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse reaction (clinically significant adverse reaction)	**Acute pancreatitis**: Acute pancreatitis may occur. Patients should be carefully monitored. If abnormalities, such as abdominal pain and increased serum amylase, are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

6 **Miscellaneous antineoplastics**

Trabectedin

Brand name	Yondelis I.V. Infusion 0.25 mg and 1 mg (Taiho Pharmaceutical Co., Ltd.)
Careful administration	Patients with previous anthracycline exposure or those with cardiac dysfunction
Important Precautions	Cardiac dysfunction may occur. Heart function test, such as echocardiography (including measurement of left ventricular ejection fraction [LVEF]) should be performed periodically before and during treatment with this drug. Clinical cardiac signs or symptoms should be carefully monitored.
Adverse reaction (clinically significant adverse reaction)	**Cardiac dysfunction**: Cardiac dysfunction, such as congestive cardiac failure and decreased LVEF, may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as dose reduction, drug suspension, or discontinuation should be adopted.

7 **Antivirals**

Oseltamivir phosphate

Brand name	Tamiflu Capsules 75, Tamiflu Dry Syrup 3% (Chugai Pharmaceutical Co., Ltd.)
Adverse reaction (clinically significant adverse reaction)	Haemorrhagic colitis and ischaemic colitis: Haemorrhagic colitis or ischaemic colitis may occur. If abnormalities, such as bloody stool and haemorrhagic diarrhea, are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

8

Flu medication and oral drug for rhinitis (OTC)

Products containing pseudoephedrine hydrochloride and pseudoephedrine sulfate (OTC drugs)

Brand name	New Long Acting S. Tac Nyscaps (Sato Yakuhin Kogyo Co., Ltd.), and the others
Consultation	If the following symptoms are observed after taking this drug, these may be adverse reactions, so immediately discontinue the use of this drug, and show this document to your physician, pharmacist, or registered salesperson for a consultation. The following serious symptoms occur in rare cases. In such a case, immediately seek medical aid. **Acute generalised exanthematous pustulosis**; Some symptoms, such as hyperthermia, widespread skin rash/redness, small pimples (small pustules) on reddened skin, general malaise, anorexia, may persist or suddenly worsen.

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 the 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 April 30, 2016)

◎: Products for which EPPV was initiated after April 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Luliconazole Luconac Solution 5% *1	Sato Pharmaceutical Co., Ltd.	April 25, 2016
◎	Progesterone Luteum Vaginal Suppository 400 mg	Aska Pharmaceutical Co., Ltd.	April 21, 2016
◎	Evolocumab (Genetical Recombination) Repatha SC Injection 140 mg syringe, 140 mg pen	Amgen Astellas BioPharma K.K.	April 21, 2016
◎	Ibandronate Sodium Hydrate Bonviva Tablets 100 mg	Chugai Pharmaceutical Co., Ltd.	April 21, 2016
	Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg *2	Shionogi & Co., Ltd.	March 18, 2016
	Eribulin Mesilate Halaven Intravenous Injection 1 mg*3	Eisai Co., Ltd.	February 29, 2016
	Risperidone Risperdal Tablets, 1 mg, 2 mg, Fine Granules 1 %, Risperdal OD Tablets 0.5 mg 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL *4	Janssen Pharmaceutical K.K.	February 29, 2016
	Rituximab (Genetical Recombination) Rituxan Injection 10 mg/mL*5	Zenyaku Kogyo Co., Ltd.	February 29, 2016
	Progesterone Utrogestan vaginal capsules 200mg	Fuji Pharma Co., Ltd.	February 18, 2016
	Indium pentetreotide (^{111}In) OctreoScan Kit for Intravenous Use	FUJIFILM RI Pharma Co., Ltd.	January 27, 2016
	Esflurbiprofen/Mentha oil Loqoa Tape	Taisho Pharmaceuticals Co., Ltd.	January 21, 2016
	Bosentan hydrate Tracleer 32 mg dispersible tablets for pediatrics	Actelion Pharmaceuticals Japan Ltd.	January 12, 2016
	Ozenoxacin Zebiax Lotion 2%	Maruho Co., Ltd.	January 7, 2016
	Vandetanib Caprelsa Tablets 100 mg	AstraZeneca K.K.	December 24, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
infliximab (genetical recombination) Remicade Intravenous Infusions 100 mg[*6]	Mitsubishi Tanabe Pharma Corporation	December 21, 2015
Apixaban Eliquis Tablets 2.5 mg, 5 mg[*7]	Bristol-Myers K.K.	December 21, 2015
nivolumab (genetical recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*8]	Ono Pharmaceutical Co., Ltd.	December 17, 2015
leuprorelin acetate Leuplin PRO Injections Kit 22.5 mg	Takeda Pharmaceutical Co., Ltd.	December 15, 2015
absorbed diphtheria-purified pertussis-tetanus- inactivated polio (salk vaccine) combined vaccine Square Kids Subcutaneous Injections Syringe	Kitasato Daiichi Sankyo Vaccine Co., Ltd.	December 9, 2015
venlafaxine hydrochloride Effexor SR Capsules 37.5 mg, 75 mg	Pfizer Japan Inc.	December 8, 2015
Trabectedin Yondelis Intravenous Infusions 0.25 mg, 1 mg	Taiho Pharmaceutical Co., Ltd.	December 7, 2015
Rivaroxaban Xarelto Fine Granules 10 mg, 15 mg[*9]	Bayer Yakuhin, Ltd.	December 7, 2015
None Miticure House Dust Mite Sublingual Tablets 3,300 JAU, 10,000 JAU	Torii Pharmaceutical Co., Ltd.	December 3, 2015
tiotropium bromide hydrate Spiolto Respimat 28 puffs	Nippon Boehringer Ingelheim Co., Ltd.	December 3, 2015
Lusutrombopag Mulpleta Tablets 3 mg	Shionogi & Co., Ltd.	December 1, 2015
Levetiracetam E Keppra Intravenous Infusions 500 mg	UCB Japan Co., Ltd.	December 1, 2015
insulin degludec (genetical recombination) / insulin aspart (genetical recombination) Ryzodeg FlexTouch	Novo Nordisk Pharma Ltd.	December 1, 2015
sucroferric oxyhydroxide P-TOL Chewable Tablets 250 mg, 500 mg	Kissei Pharmaceutical Co., Ltd.	November 27, 2015
ombitasvir hydrate/paritaprevir hydrate/ritonavir Viekirax Combination Tablets	AbbVie G.K.	November 26, 2015
glatiramer acetate Copaxone S.C. Injections 20 mg Syringe	Takeda Pharmaceutical Co., Ltd.	November 26, 2015
vildagliptin/metformin hydrochloride EquMet Combination Tablets LD and HD	Novartis Pharma K.K.	November 26, 2015
Omarigliptin Marizev Tablets 12.5 mg, 25 mg	MSD K.K.	November 26, 2015
None Actair House Dust Mite Sublingual Tablets 100 units (IR) and 300 units (IR)	Shionogi & Co., Ltd.	November 19, 2015
Rivaroxaban Xarelto Tablets 10 mg, 15 mg[*9]	Bayer Yakuhin, Ltd.	September 24, 2015

*1 Nail tinea
*2 Pain associated with chronic lumbago
*3 Malignant soft tissue sarcoma
*4 Irritability associated with autism spectrum disorder in childhood
*5 Prophylaxis of antibody-related type rejection in the ABO blood group incompatibility transplant of kidney and liver transplants
*6 Acute stage of Kawasaki's disease
*7 Treatment of venous thromboembolism [deep vein thrombosis (DVT) and pulmonary embolism (PE)], and prophylaxis of recurrent DVT and PE
*8 Unresectable advanced/recurrent non-small cell lung cancer
*9 Treatment of DVT and PE, and prophylaxis of recurrent DVT and PE