Pharmaceuticals and Medical Devices Safety Information

No. 348 November 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. 347 October 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
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BNP	Brain natriuretic peptide
CK	Creatine kinase
CK-MB	Creatine kinase MB
CRP	C-reactive protein
CT	Computed tomography
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HbA1c	Hemoglobin A1c
JSHP	Japanese Society of Hospital Pharmacists
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MHLW	Ministry of Health, Labour and Welfare
PaO_2	Arterial oxygen partial pressure
PLT	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
RBC	Red blood cell count
SD	Safety Division
SNS	Social networking service
SP-D	Surfactant protein D
SpO_2	Oxygen saturation
WBC	White blood cell count
XP	X-ray photograph

1

Initiative of Revision of the Manuals for Management of Individual Serious Adverse Drug Reactions

1. Manuals for Management of Individual Serious Adverse Drug Reactions

The Manuals for Management of Individual Serious Adverse Drug Reactions were compiled from FY 2005 to FY 2010 by the committee on the comprehensive actions for serious adverse drug reactions who reviewed and compiled the drafts prepared by manual preparation committees organized in related academic societies through discussions with the Japanese Society of Hospital Pharmacists (JSHP) as entrusted by MHLW. The drafts were prepared with reference to academic papers, various guidelines, health and labour sciences research project reports, PMDA health and welfare service reports, etc. At present, the manuals are available for a total of 75 diseases.

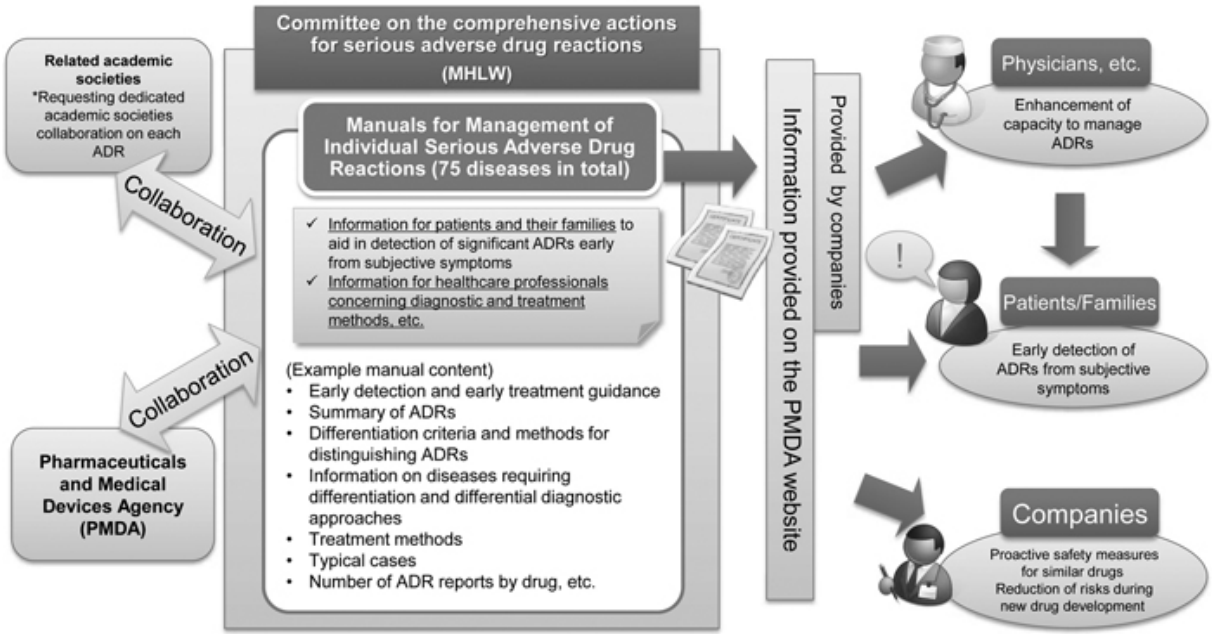
Basic sections of the manuals are as follows:

(1) For patients:

Summary of adverse drug reactions (ADRs), initial symptoms, and critical points for early detection/early action that patients or their families should know are described in plain language for easy understanding.

(2) For healthcare professionals

- Points for early detection and early action
  (Initial symptoms, predilection time, actions to be taken by healthcare professionals, etc. as critical points are described to contribute to early detection of and early actions for ADRs by healthcare professionals such as physicians and pharmacists.)
- Summary of ADRs
- Differentiation criteria (methods for distinguishing) ADRs
  (Criteria [methods] [differentiating] to determine whether symptoms encountered in clinical practice are ADRs are described.)
- Diseases that need to be distinguished and methods for distinguishing them
  (Summary of other diseases or ADRs that show symptoms, etc. similar to relevant ADRs and methods for distinguishing [differentiating] them are described.)
- Treatment methods
  (Main treatment methods are described as actions to take in case ADRs occur.)
- Typical cases
  (ADRs described in these manuals are generally are, and there are few physicians and pharmacists with experience of such ADRs. Therefore, typical cases are described in a way that show the time course to the extent possible.)
- Cited literature /reference materials
  (As references for further information gathering related to relevant ADRs, literature cited and reference literature papers related to relevant ADRs that were used for the preparation of the manuals are listed.)



2. Initiative of Revision

Approximately 10 years have passed since the preparation of major manuals, and consequently, descriptions may sometimes be obsolete. To promote further utilization, the initiative was started in FY 2016 for revision/update implemented in 5 years taking into account the latest knowledge with the cooperation of related academic societies, etc. similarly to the initial preparation of manuals.

3. Progress of Revision

In FY 2016, the Japanese Dermatological Association reviewed the Manuals for Management of Individual Serious Adverse Drug Reactions for Stevens-Johnson syndrome and toxic epidermal necrolysis for revision. The discussion was carried out in response to the revision of related guidelines of this association, to reflect the revision in the manuals. The main changes are as follows.

- Criteria for distinguishing and methods for distinguishing ADRs were updated in line with the guidelines of the association.
- Five-day continuous administration of human immunoglobulin preparations at 400 mg/kg/day was added to treatment methods.
- Old cases listed in the summary of typical cases were replaced with new cases.
- Cited literature papers were replaced with reference papers that reflect the latest knowledge.
- Reference 1 (number of reports of ADRs under Article 68-10 of the Pharmaceuticals and Medical Devices Act) and Reference 2 (Medical Dictionary for Regulatory Activities [MedDRA/J]) in the manuals were updated.

In addition, to decide the priority of manuals to be revised in and after FY 2017, a questionnaire was completed by the academic societies to gather opinions regarding the necessity/unnecessity of revision for existing manuals and opinions regarding manuals to be newly prepared.

4. How Revision Will Proceed

Regarding the plan for revision of the manuals in and after FY 2017, the following matters were taken into account when considering the priority for organizing working groups for manual revision, etc. dedicated to individual academic societies, based on the results of the questionnaire:

(1) Priorities

- Manuals that need to be harmonized with guidance/guidelines of academic societies that have been revised since their preparation.
- Manuals that need to be harmonized with current definitions of diseases which have been altered since their preparation
- New guidelines to deal with serious ADRs

(2) Other considerations

- Manuals that will need to be harmonized with revision of guidance/guidelines, etc. or modification of definitions of diseases which are currently reviewed (or will be reviewed in the near future).
- Manuals for which academic societies have expressed their opinions that no particularly substantial revision is expected.
  Regarding those for which there is an opinion that revision is not necessary or only factual update on an as needed basis should be sufficient, the MHLW and the JSHP will handle such update to Reference 1 (number of reports of ADRs under Article 68-10 of the Pharmaceuticals and Medical Devices Act) and Reference 2 (MedDRA/J) in the manuals in a sequential manner.

Based on this concept, priority is divided into four segments (A: Scheduled start in FY 2017, B: Scheduled start in or after FY 2018 (high priority), C: Scheduled start in or after FY 2018 (intermediate priority), and D: Simple update). The number of manuals in each segment is as follows.

Table 1. Number of manuals in each segment

A: Scheduled start in FY 2017	Revision	12
	New	2
B: Scheduled start in or after FY 2018 (high priority)	Revision	22
	New	6
C: Scheduled start in or after FY 2018 (intermediate priority)	Revision	15
D: Simple update	Revision	23

*For details, refer to the materials provided for the 9th meeting of the committee on the comprehensive actions for serious adverse drug reactions.
http://www.mhlw.go.jp/stf/shingi2/0000164763.html (only available in Japanese language)

Based on these segments, the revision will be made in consideration of the capacity of academic societies involved in the revision of the manuals.

2

Prevention of Accidents with Electric Massagers for Household Use

1. Introduction

Fatal accidents due to inappropriate use of electric massagers for household use have occurred repeatedly. Particularly when roller-type electric massagers are used without the cloth cover or with the cloth cover torn due to age-related degradation, the collar of clothes or the like may get caught, thereby squeezing the neck of the user leading to death from suffocation. In addition, there was a case reported that user's hair got caught in the roller part and could not be removed until the hair was cut off. When you use an electric massager for household use, please read the instruction manual carefully and use it correctly.

Never use electric massagers for household use without the cover or with the cover torn because it is very dangerous.

2. Past Fatal Accidents

The following is a summary of fatal cases reported so far to MHLW as caused by inappropriate use of electric massagers for household use.

(1)	Brand name of product	1. Albi shape-up roller 2. Shape-up roller II
	Marketing authorization holder	Matoba Electric Manufacturing Co., Ltd.
	Sales period	1. From 1983 to 1990 (Number of units sold: approx. 420 000) 2. From July 1988 to 1996 (Number of units sold: approx. 360 000)
	Outline of accident	The massager was used with the cloth cover removed and user's clothes got caught, causing suffocation and death.
	Year of accident, etc.	1999: One case in Tochigi prefecture 2003: One case in Kagawa prefecture 2008: One case in Hokkaido (The above cases were made public on December 16, 2008) 2012: One case in Aichi prefecture (made public on May 10, 2012) 2014: One case in Yamanashi prefecture (made public on June 23, 2014) 2017: One case in Hokkaido (made public on August 1, 2017)
(2)	Brand name of product	Handy Massager GM-2 (nick name: Momita-kun)
	Marketing authorization holder	Fuji Medical Instruments MFG. Co., Ltd.
	Sales period	From 1995 to 2003 (Number of units sold: approx. 110 000)
	Outline of accident	The massager was used with the cloth cover torn and the user's scarf got caught, causing suffocation and death.
	Year of accident, etc.	2010: One case in Shizuoka prefecture (made public on February 5, 2010)

Regarding the above accidents, related information can also be found on the MHLW's website.

3. Request for Discontinuation/Recall of Products

Following the occurrence of the fatal accidents reported so far, Matoba Electric Manufacturing Co., Ltd. is requesting discontinuation and recall of the two products (Albi shape-up roller and Shape-up roller II) that caused the accidents by means such as preparing and distributing the material for provision of information attached on the next page (only available in Japanese language).

To prevent similar accidents, it is extremely important to widely call attention for households that have the products concerned. The MHLW is also requesting prefectural governments, the Consumer Affairs Agency, the Japan Pharmaceutical Association, and the Japan Home-Health Apparatus Industrial Association to provide their cooperation, and is also making efforts to call attention through media such as websites and SNS.

4. To Readers

If you have any of the products subjected to recall, please discontinue use immediately and contact Matoba Electric Manufacturing Co., Ltd. (toll free: 0120-01-2251; reception hours: 9:00-17:00 weekdays). For the material for provision of information attached on the next page, the electronic medium can be downloaded from the MHLW's website. If possible, please cooperate in the publicity activities, such as posting the information at medical institutions, stores, etc.

(MHLW's website)
"Proper use of electric massagers for household use (Calling attention)"
http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000048807.html (only available in Japanese language)

(Related notification)
"Publicity, etc. regarding the prevention of accidents with electric massagers for household use"
PSEHB/SD Notification No. 1016-1, by the Director, Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated October 16, 2017 (Requesting cooperation) (only available in Japanese language)

! 探しています

的場電機製作所製の
家庭用ローラー式電気マッサージ器を探しています

布カバーを外した誤った使い方により、死亡事故が発生しております。
下記製品をお持ちの方は、すぐに使用を中止してご連絡願います。

通話料無料
携帯・PHS OK
0120-01-2251
※携帯・PHSからもご利用になれます。

受付時間 9:00 ～ 12:00
13:00 ～ 17:00
※土日・祝日・年末年始・弊社指定休日は除く

【対象製品は 2 機種です】

昭和 58 年 (1983 年) ～平成 8 年 (1996 年) 製造

アルビシェイプアップローラー

機種名は本体側面のラベル表示をご確認ください。

布カバーを外した状態

シェイプアップローラーⅡ

機種名は本体裏面のラベル表示をご確認ください。

布カバーを外した状態

株式会社 的場電機製作所
〒350-1101 埼玉県川越市的場 2627-5　☎049-231-2255(代表)

薬生安発 1016 第 1 号 平成 29 年 10 月 16 日　厚生労働省医薬・生活衛生局医薬安全対策課長通知
「家庭用電気マッサージ器による事故防止に関する周知等について（協力依頼)」

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated October 17, 2017, the contents of important revisions and a case summary that served as the basis for these revisions are provided in this section.

1 Levetiracetam

Brand name (name of company)	a. E Keppra Tablets 250 mg, 500 mg, E Keppra Dry Syrup 50% (UCB Japan Co., Ltd.) b. E Keppra for I.V. Infusion 500 mg (UCB Japan Co., Ltd.)
Therapeutic category	Antiepileptics
Indications	a. Partial seizures in epilepsy patients (including secondary generalized seizures) □ Concomitant therapy with other antiepileptic drugs for tonic-clonic seizures in epilepsy patients who fail to show a satisfactory response to other antiepileptic drugs b. As an alternative to levetiracetam oral tablets for the following treatments in patients who are not able to use the oral treatment temporarily: □ Partial seizures in epilepsy patients (including secondary generalized seizures); □ Concomitant therapy with other antiepileptic drugs for tonic-clonic seizures in epilepsy patients who fail to show a satisfactory response to other antiepileptic drugs

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	Neuroleptic malignant syndrome: Neuroleptic malignant syndrome may occur. If pyrexia, muscle rigidity, increased creatinine kinase (creatinine phosphokinase), tachycardia, blood pressure fluctuation, disturbed consciousness, excess sweating, increased white blood cells, etc. are observed, administration of this drug should be discontinued and appropriate measures such as cooling of the body, hydration, respiratory management, etc. should be taken. Decreased renal function with myoglobinuria may also occur.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 5 months (April 2014 to September 2017). Cases related to neuroleptic malignant syndrome: 2 cases (no fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 290 000 Launched in Japan: E Keppra Tablets 250 mg, 500 mg, September 2010 E Keppra Dry Syrup 50%, August 2013 E Keppra for I.V. Infusion 500 mg, December 2015

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 30s	Epilepsy (mental retardation)	500 mg 4 days ↓ 1000 mg 42 days ↓ 2000 mg 43 days	Neuroleptic malignant syndrome In addition to blonanserin, administration of levetiracetam 500 mg/day was started. Day 5 of administration: The dose of levetiracetam was increased to 1000 mg/day. Day 47 of administration: The dose of levetiracetam was increased to 2000 mg/day. Day 89 of administration: Day of discontinuation Day 90 of administration: Pyrexia and epileptiform muscles stiffness. The patient was admitted to the hospital because he developed a symptom in which he opened his eyes but with no response and had a facial expression like death throes. Tension was alleviated by diazepam 5 mg. The patient was diagnosed with drug-induced neuroleptic malignant syndrome. Administration of levetiracetam and blonanserin was discontinued (the preceding day was the last day of administration), and infusion was started. 2 days after discontinuation: The body temperature decreased without using an antipyretic. CK was elevated to a peak. Urine myoglobin was present. Administration of infusion was continued and CK tended to decrease. The patient uttered words, and his consciousness recovered to a nearly normal level within several days. 14 days after discontinuation: The disease remitted and subsequently resolved.

Laboratory Examination

	230 days before administration	Day 90 of administration	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	6 days after discontinuation	8 days after discontinuation
Body temperature (°C)		39.2	37.7	37.5	37.3		36.4
RBC ($\times 10^4$/μL)	486	524	487	463	447		431
Hemoglobin (g/dL)		16.4	15.0	14.3	14.0		13.7
Hematocrit (%)		46.8					
WBC (/μL)	5 000	37 700	18 000	12 500	9 800	8 500	8 700
Neutrophils (%)		92.2	85.6	81.6	78.5		83
Eosinophils (%)		0					
Basophils (%)		0.1					
Lymphocytes (%)		2.6	6.9	12.3	15.8		11.2
Monocytes (%)		5.1					
PLT ($\times 10^4$/μL)		33.3	23.7	22.4	20.0		
LDH (IU/L)		585	949	872	721	339	268
CK (IU/L)		3 807	40 128	37 870	29 712	5 956	1 418
CK-MB (IU/L)		50	0				
Serum myoglobin (ng/mL)			7 750				
CRP (mg/dL)		0.19	4.78		0.78	0.63	0.6
AST (IU/L)	16	60	491	599	566		100
ALT (IU/L)	14	46	90	122	135		139

Suspected concomitant medications: blonanserin
Concomitant medications: polaprezinc, bifidobacterial preparation

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Epilepsy (hypertension, viral encephalitis, mental impairment disorders)	1000 mg 4 days	**Neuroleptic malignant syndrome** Day 1 of administration Start of administration Day 4 of administration Due to twitches and tremor in the upper limbs, the patient visited the emergency outpatient unit. As neuroleptic malignant syndrome was suspected, administration of dantrolene sodium hydrate was started. Administration of levetiracetam was discontinued. 5 days after discontinuation The patient was discharged from the hospital because he recovered.

Laboratory Examination

	445 days before administration	Day 1 of administration	Day 4 of administration (Day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	7 days after discontinuation
Body temperature (°C)			39.8 37.9	37.8	37.2	36.3	36.7	
Pulse rate (beats/min)			142 103	98	80	70	70	
Blood pressure (mmHg)				153/99	112/73	120/91	123/72	
RBC ($\times 10^4$/μL)	418	429	415	390			346	367
Hemoglobin (g/dL)	13.7	14.6	14.4	13.3			11.8	12.5
Hematocrit (%)	41.4	44.0	43.4	42.3			35.7	37.5
WBC (/μL)	4 000	8 700	7 400	5 200			3 000	3 800
Neutrophils (%)			75.4					
Eosinophils (%)			0					
Basophils (%)			0.1					
Lymphocytes (%)			18.5					
Monocytes (%)			6					
PLT ($\times 10^4$/μL)	12.9	12.6	9.9	8.2			8.5	13.6
LDH (IU/L)	224	503		532			438	469
CK (IU/L)			1 703	844			316	152
CRP (mg/dL)			0.03					
AST (IU/L)	19	25	51	36			17	19
ALT (IU/L)	20	22	34	33			19	25

Concomitant medications: carbamazepine, amlodipine besilate, teprenone, tocopherol nicotinate

2 Linagliptin

Brand name (name of company)	Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic category	Antidiabetic agents
Indications	Type 2 diabetes mellitus

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids 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 3 years and 5 months (April 2014 to September 2017).
Cases related to interstitial pneumonia : 4 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 880 000

Launched in Japan: September 2011

Case Summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/ Age</th><th>Reason for use (complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>1</td><td>Female
70s</td><td>Type 2 diabetes mellitus (hypothyroidism, myocardial ischaemia, chronic renal failure)</td><td>5 mg
196 days</td><td>Interstitial pneumonia
Past history: Breast cancer
Day 1 of administration: Administration of linagliptin was started.
Around 5 months of administration: Cough and shortness of breath occurred. Interstitial pneumonia occurred.
Day 187 of administration: Interstitial pneumonia was noted on CT at another hospital. High KL-6 level and high LDH level
Day 194 of administration: The patient was referred to this hospital. Fine crackles were heard on inspiration.
Day 196 of administration (Day of discontinuation): Administration was discontinued.
14 days after discontinuation: On chest CT, interstitial pneumonia disappeared. KL-6 decreased. The patient recovered from interstitial pneumonia. Due to high blood sugar levels, the patient was admitted to the internal medicine department for diabetes control.</td></tr>
<tr><td colspan="5">Laboratory Examination
<table>
<tr><th></th><th>Day 194 of administration</th><th>Day 196 of administration (Day of discontinuation)</th><th>14 days after discontinuation</th><th>15 days after discontinuation</th><th>22 days after discontinuation</th></tr>
<tr><td>LDH (IU/L)</td><td>-</td><td>291</td><td>285</td><td>-</td><td>332</td></tr>
<tr><td>SpO_2 (%)</td><td>95</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>KL-6 (U/mL)</td><td>-</td><td>2 150</td><td>1 690</td><td>1 690</td><td>1 360</td></tr>
<tr><td>Blood glucose (mg/dL)</td><td>-</td><td>-</td><td>600</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td colspan="5">Concomitant medications: aspirin, atorvastatin calcium hydrate, dried thyroid, insulin degludec (genetical recombination), liraglutide (genetical recombination)</td></tr>
</table>

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Type 2 diabetes mellitus (chronic kidney disease, malignant lung neoplasm, unstable angina, dyslipidemia, myocardial infarction)	5 mg 10 days	**Interstitial pneumonia, respiratory failure** Past history: Myocardial infarction Day 1 of administration: Due to HbA1c 7.7%, the patient visited the diabetes department for diabetes control. In addition to 1400 kcal and limitation of salt intake to 6 g, administration of linagliptin was started. Date unknown: Dyspnoea occurred gradually. Day 10 of administration (Day of discontinuation): When chest CT was performed, diffuse ground glass opacities appeared in both lungs. As SpO_2 90% (room air) and PaO_2 57.8 Torr confirmed respiratory failure, the patient was admitted to the hospital urgently on the same day. Interstitial shadows appeared. On the same day, intravenous drip infusion of ceftriaxone and azithromycin was started. Steroids were administered systemically for respiratory failure. Administration of linagliptin, aspirin and clopidogrel sulfate was discontinued. 5 days after discontinuation: Even with drip infusion of antagonists, there was no improvement. Prednisolone sodium succinate 55 mg/day for injection was started. In chest X-ray photos, there was no improvement of the shadows in both lungs. 7 days after discontinuation: Aspirin and clopidogrel sulfate were resumed. 8 days after discontinuation: Oxygenation improved (SpO_2: 97%, nasal cannula 3L/min). The dose of prednisolone sodium succinate for injection was reduced to 45 mg. On the same day, concomitant use of sulfamethoxazole/trimethoprim combination tablets was started. 9 days after discontinuation: The patient withdrew from oxygen administration. SpO_2: 97% (room air) 10 days after discontinuation: The dose of prednisolone sodium succinate for Injection was reduced to 30 mg/day. 13 days after discontinuation: Prednisolone 25 mg/day was orally taken. 16 days after discontinuation: The dose of prednisolone was reduced to 20 mg/day. 21 days after discontinuation: The dose of prednisolone was reduced to 15 mg/day. 26 days after discontinuation: The dose of prednisolone was reduced to 10 mg/day, and the patient was discharged from the hospital on the same day. Interstitial pneumonia remitted (inflammatory changes remained on XP). 33 days after discontinuation: The patient re-visited the outpatient unit. There was no worsening of the shadows in chest X-ray. The dose of prednisolone was reduced to 5 mg/day. 54 days after discontinuation: Respiratory failure remitted.

Laboratory Examination

	52 days before administration	Day 6 of administration	Day 10 of administration (Day of discontinuation)	1 day after discontinuation	2 days after discontinuation	9 days after discontinuation	16 days after discontinuation	26 days after discontinuation	33 days after discontinuation
LDH (IU/L)	-	Nituit	600	-	-	323	236	288	310
KL-6 (U/mL)	194	308	-	-	-	-	-	-	-
CRP (mg/dL)	-	-	9.951	-	-	1.078	0.089	0.029	0.015
SP-D (ng/mL)	-	-	-	-	367.0	-	205.0	96.1	-
BNP (pg/mL)	-	-	-	202.6	-	-	-	-	-
β-D-glucan (pg/mL)	-	-	-	<6.0	-	-	-	-	-

Concomitant medications: aspirin, clopidogrel sulfate, rabeprazole sodium, bisoprolol fumarate, atorvastatin calcium hydrate, amlodipine besilate, ethyl icosapentate, sodium ferrous citrate, calcium polystyrene sulfonate

4

Revision of Precautions (No. 289)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs in accordance with the Notifications dated October 17, 2017

1 Antiepileptics

Levetiracetam

Brand name	a. E Keppra Tablets 250 mg, 500 mg, E Keppra Dry Syrup 50% (UCB Japan Co., Ltd.) b. E Keppra for I.V. Infusion 500 mg (UCB Japan Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	Neuroleptic malignant syndrome: Neuroleptic malignant syndrome ma occur. If pyrexia, muscle rigidity, increased creatinine kinase (creatinin phosphokinase), tachycardia, blood pressure fluctuation, disturbed consciousness, excess sweating, increased white blood cells, etc. are observed, administration of this drug should be discontinued and appropriate measures such as cooling of the body, hydration, respirato management, etc. should be taken. Decreased renal function with myoglobinuria may also occur.

2 Digestive organ agents-Miscellaneous

Chlorhexidine hydrochloride/diphenhydramine salicylate/hydrocortisone acetate/benzalkonium chloride concentrated solution 50

Brand name	Despakowa Oral Cream (Kowa Company, Ltd.)
Important Precautions	In order to predict reactions such as shock or anaphylaxis, a sufficient medical interview should be performed regarding the history of hypersensitivity to chlorhexidine preparations and for predisposition to drug hypersensitivity in advance.
Adverse reactions (clinically significant adverse reactions)	Shock, anaphylaxis: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if decreased blood pressure, urticaria, dyspnoea, etc. are observed, the use of this drug should be discontinued immediately and appropriate measures should be taken.

3 Local Antimicrobial agents

Chlorhexidine gluconate (prescription drugs)

Brand name	Hibitane gluconate solution 20% (Dainippon Sumitomo Pharma Co., Ltd.), Acesclean hand disinfection solution 0.2% (Nichi-Iko Pharmaceutical Co., Ltd.), Chlorhexidine gluconate EW 5% “NP” for disinfection solution (Nipro Corporation), and others
Important Precautions	In order to predict reactions such as shock or anaphylaxis, a sufficient medical interview should be performed regarding the history of hypersensitivity to chlorhexidine preparations and for predisposition to drug hypersensitivity in advance.
Adverse reactions (clinically significant adverse reactions)	Shock, anaphylaxis: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if decreased blood pressure, urticaria, dyspnoea, etc. are observed, the use of this drug should be discontinued immediately and appropriate measures should be taken.

4 **Antidiabetic agents**

Linagliptin

Brand name	Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

5 **Acting mainly on gram-positive and gram-negative bacteria**
Antibiotics-Miscellaneous

a. Amoxicillin hydrate
b. Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
c. Vonoprazan fumarate/amoxicillin hydrate/metronidazole
d. Rabeprazole sodium/amoxicillin hydrate/clarithromycin
e. Rabeprazole sodium/amoxicillin hydrate/metronidazole
f. Lansoprazole/amoxicillin hydrate/clarithromycin
g. Lansoprazole/amoxicillin hydrate/metronidazole

Brand name	a. Sawacillin Capsules 125 and 250, Sawacillin Fine Granules 10%, Sawacillin Tablets 250 (Astellas Pharma Inc.), Pasetocin Capsules 125 and 250, Pasetocin Fine Granules 10%, Pasetocin Tablets 250 (Aspen Japan K.K.), and others b. Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited) c. Vonopion Pack (Takeda Pharmaceutical Company Limited) d. Rabecure Pack 400, 800 (Eisai Co., Ltd.) e. Rabefine Pack (Eisai Co., Ltd.) f. Lansap 400, 800 (Takeda Pharmaceutical Company Limited) g. Lampion Pack (Takeda Pharmaceutical Company Limited)
Adverse reactions (clinically significant adverse reactions)	Granulocytopenia, thrombocytopenia: Granulocytopenia or thrombocytopenia may occur. Patients should be carefully monitored by means such as periodically performing tests. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6 **Acting mainly on gram-positive and gram-negative bacteria**

Potassium clavulanate/amoxicillin hydrate

Brand name	Augmentin Combination Tablets 125 SS and 250 RS, Clavamox Combination Dry Syrup for pediatric (GlaxoSmithKline K.K.)
Adverse reactions (clinically significant adverse reactions)	Agranulocytosis, granulocytopenia, thrombocytopenia: Agranulocytosis, granulocytopenia, thrombocytopenia may occur. Patients should be carefully monitored by means such as performing blood tests. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

7 **Synthetic antibacterials**

Moxifloxacin hydrochloride (oral dosage form)

Brand name	Avelox Tablets 400 mg (Bayer Yakuhin, Ltd.)
Adverse reactions (clinically significant adverse reactions)	Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored, and if myalgia, feeling of weakness, increased creatinine kinase (creatinine phosphokinase), increased blood and urinary myoglobin, etc. are observed, administration of this drug should be discontinued and appropriate measures should be taken. Attention should be paid to the onset of acute kidney injury due to rhabdomyolysis.

8 **Over the counter drugs**

a. Products containing chlorhexidine gluconate
b. Products containing chlorhexidine hydrochloride

Brand name	a. Oronine H Ointment (Otsuka Pharmaceutical Factory, Inc.), Memo-A (S S Pharmaceutical Co., Ltd.), Stericlon 0.05% Cotton Ball P (KENEI Pharmaceutical Co., Ltd.), and others. b. Preser S Ointment (Taisho Pharmaceutical Co., Ltd.), Tamuchinki Powder Spray C (Kobayashi Pharmaceutical Co., Ltd.), Shionogi D Ointment (Shionogi Healthcare & Co., Ltd.), and others
When not to use the product	This product should not be used in the following persons: Patients who have had an allergic symptom to this drug, its ingredients, or chlorhexidine.
Consultation	If the following symptoms are observed after using this drug, these may be adverse reactions, so immediately discontinue the use, and show this document to your physician, pharmacist, or registered sales person for a consultation. The following serious symptoms may occur in rare cases. In such cases, immediately seek medical aid: Shock (anaphylaxis): Symptoms, such as itching of skin, urticaria, hoarseness, sneezing, itchy throat, breathing difficulties, palpitations, and clouding of consciousness may occur immediately after use.

9 **Quasi- drugs**

a. Products containing chlorhexidine gluconate
b. Products containing chlorhexidine hydrochloride

Brand name	a. Mackin α (Tamagawa-Eizai Co., Ltd.), OraLeaf (KENEI Pharmaceutical Co., Ltd.), and others b. SunStar medicated toothpaste CH (Sunstar Inc.), Gel Coat <F> + (Smoca Dentifrice Co., Ltd.), CH Gel Guard (NIPPON ZETTOC Co., Ltd.), and others
Precautions	As Precautions, the following texts should be added to the package inserts, outer container, or wrapper of the product. (1) Persons who have had an allergic symptom to these products, their ingredients, or chlorhexidine should not use these products. (2) Serious symptoms of shock (anaphylaxis) may occur in rare cases. If experiencing symptoms such as urticaria, breathing difficulties, or clouding of consciousness immediately after using these products, discontinue the use of the product at once and seek medical aid. Persons who have had allergic symptoms to drugs or other should exercise particular caution and consult health care professionals prior to use.

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 Marketing Authorization Holder (MAH) is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

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

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Quetiapine fumarate[*1] Bipresso Extended Release Tablets 50 mg, 150 mg	Astellas Pharma Inc.	October 27, 2017
◎	Sildenafil citrate Revatio Tablets 20 mg	Pfizer Japan Inc.	September 27, 2017
◎	Nusinersen sodium[*2] Spinraza Intrathecal Injection 12 mg	Biogen Japan Ltd.	September 22, 2017
◎	Lyophilized human prothrombin complex concentrate Kcentra for I.V. Injection 500, 1000	CSL Behring K.K.	September 19, 2017
◎	Teneligliptin hydrobromide hydrate/ canagliflozin hydrate Canalia Combination Tablets	Mitsubishi Tanabe Pharma Corporation	September 7, 2017
◎	Amenamevir Amenalief Tab. 200 mg	Maruho Co., Ltd.	September 7, 2017
◎	Baricitinib Olumiant Tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	September 1, 2017
	Pralatrexate Difolta Injection 20 mg	Mundipharma K.K.	August 30, 2017
	Nusinersen sodium Spinraza Intrathecal injection 12 mg	Biogen Japan Ltd.	August 30, 2017
	Leuprorelin acetate[*3] Leuplin SR for Injection Kit 11.25 mg	Takeda Pharmaceutical Company Limited	August 25, 2017
	Eltrombopag olamine[*4] Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	August 25, 2017
	Lyophilized human antithrombin III concentrate[*5] Kenketu Nonthron 500 for Injection, 1500 for Injection	Nihon Pharmaceutical Co., Ltd.	August 25, 2017
	Florbetapir (^{18}F) Amyvid Injection	Fujifilm RI Pharma Co., Ltd.	August 21, 2017
	Clobetasol propionate	Maruho Co., Ltd.	July 11, 2017

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	Comclo Shampoo 0.05%		
	Denosumab (genetical recombination) [*6] Pralia Subcutaneous Injection 60 mg Syringe	Daiichi Sankyo Company, Limited	July 3, 2017
	Fluvoxamine maleate (1) Luvox Tablets 25 mg, 50 mg, 75 mg (2) Depromel Tablets 25 mg, 50 mg, 75 mg	(1) AbbVie GK (2) Meiji Seika Pharma Co., Ltd.	July 3, 2017
	Hydromorphone hydrochloride Narurapid Tablets 1 mg, 2 mg, 4 mg, Narusus Tablets 2 mg, 6 mg, 12 mg, 24 mg	Daiichi Sankyo Propharma Co., Ltd.	June 19, 2017
	Naldemedine tosilate Symproic Tablets 0.2 mg	Shionogi & Co., Ltd.	June 7, 2017
	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) [*7] (1) Stelara Intravenous Infusion 130 mg, (2) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	May 24, 2017

*1 Depressive symptoms in bipolar disorder

*2 Spinal muscular atrophy

*3 Suppression of progression of congenital bulbospinal muscular atrophy

*4 Aplastic anaemia

*5 Portal vein thrombosis associated with decreased antithrombin III

*6 Suppression of progression of bone erosion associated with rheumatoid arthritis

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