Pharmaceuticals and Medical Devices Safety Information

No. 299 February 2013

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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) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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

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

Pharmaceuticals and Medical Devices Safety Information
No. 299 February 2013

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

[Outline of Information]

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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

ADRs	Adverse drug reactions
BUN	Blood urea nitrogen
CK (CPK)	Creatine kinase (Creatine phosphokinase)
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HJ	Hugh-Jones
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IU	International unit
JCS	Japan Coma Scale
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal antiinflammatory drug
PS	Performance status
RA	Respiratory airflow
SJS	Stevens-Johnson syndrome
SpO2	Oxygen saturation
SS-A/Ro	Sjögren's syndrome A/Ro
SS-B/La	Sjögren's syndrome B/La
WAO	World Allergy Organization
WBC	White blood cell count

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Utilization of the PMDA Medical Safety Information

1. Introduction

PMDA has issued the "PMDA Medical Safety Information" to extensively provide healthcare professionals with information about frequently reported "near-miss" incidents, accidents and adverse events related to drugs and medical devices since fiscal year (FY) 2007. Information about the start of posting "PMDA Medical Safety Information" on the PMDA website was presented in the PMDSI No. 241 dated November 2007, and information about its subsequent issuances was introduced in the PMDSI No. 262 dated October 2009. This section again explains about the "PMDA Medical Safety Information" and how to access it to encourage its utilization for ensuring the safe use of drugs and medical devices.

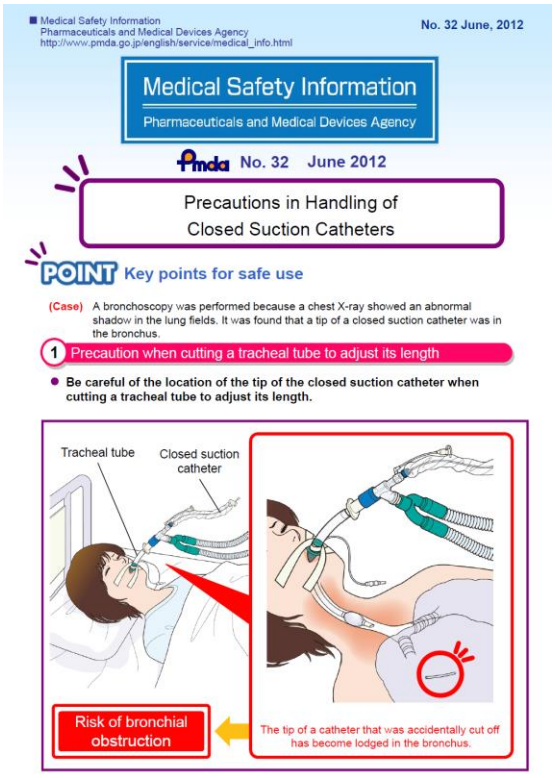
2. The "PMDA Medical Safety Information"

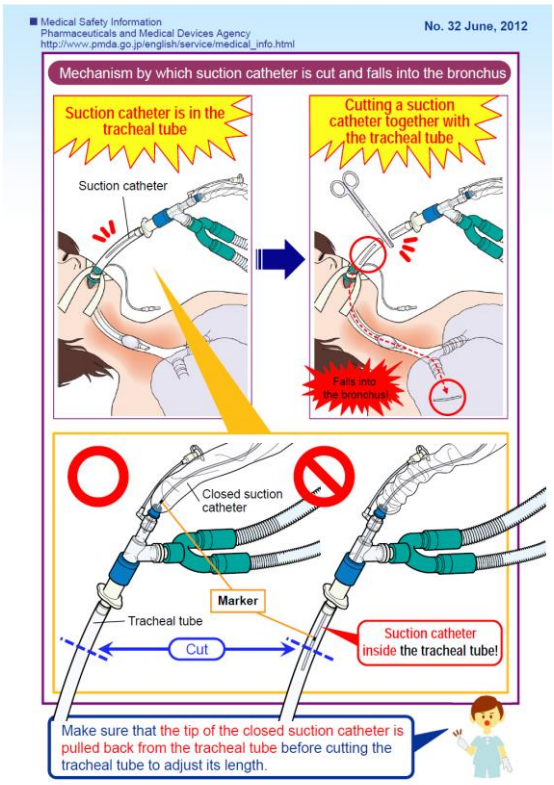
The "PMDA Medical Safety Information" provides precautions to healthcare professionals about "near-miss" incidents, accidents and adverse events related to drugs and medical devices which have been frequently reported or lead to measures such as revisions of package inserts to ensure medical safety.

Figure 1 shows an example of the "PMDA Medical Safety Information." The aims of the "PMDA Medical Safety Information" are to provide precautions to be taken for ensuring safe use of drugs and medical devices to healthcare professionals. For this purpose, it provides information in an easy-to-understand manner with illustrations and pictures. The "PMDA Medical Safety Information" has been prepared and issued by the PMDA considering the opinions of healthcare professionals including physicians, pharmacists, nurses, and clinical engineers, specialists such as those in the field of ergonomics, as well as industry organizations including marketing authorization holders (MAHs) of drugs or medical devices.

Table 1 lists the currently available "PMDA Medical Safety Information."

Figure 1 PMDA Medical Safety Information (Example: No. 34 Precautions in Handling of Glycerin Enemas)





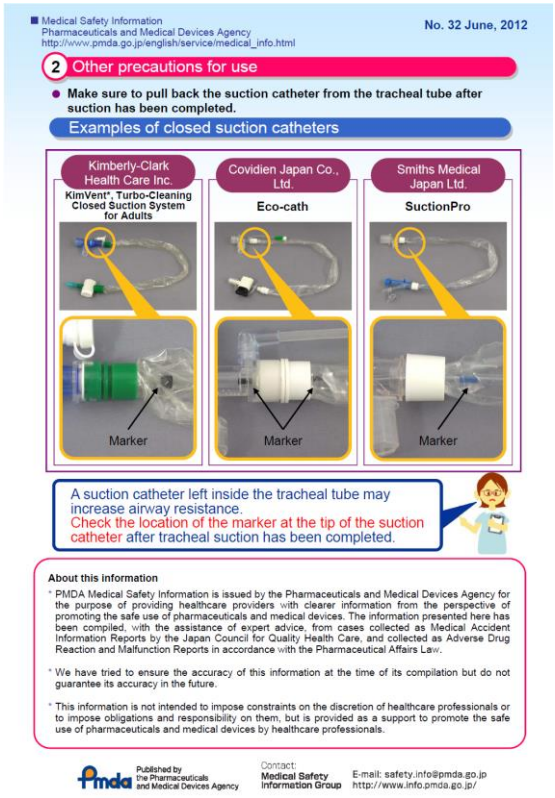


Table 1 Currently available PMDA Medical Safety Information (as of February 1, 2013)

No	Issued in	Title
1	November 2007	Points to note in case of obstruction of feeding tube
2	November 2007	Recall of Resuscitators
3	January 2008	Precautions against improper connection of speech valves etc. to tracheostomy tubes
4	June 2008	Precautions against smoking and use of fire in Long-term Oxygen Therapy (LTOT)
5	June 2008	Handling of lancing devices for obtaining blood samples
6	October 2008	Precautions against misuse (overdose) of antirheumatic methotrexate preparations
7	January 2009	Precautions in Artificial Respiration (No.1)
8	February 2009	Compatibility between a "Type A" Needle (JIS T 3226-2) and a Insulin Pen (JIS T 3226-1)
9	February 2009	Recall of Jackson-Rees Circuits
10	May 2009	Good Management & Maintenance of Automated External Defibrillators (AEDs)
11	August 2009	Precautions in Artificial Respiration (No.2)
12	September 2009	Misconnection of tourniquet cuff
13	October 2009	Medical Gas Mix-Ups
14	February 2010	Precautions in Handling of Electric Scalpels (Part 1)
15	March 2010	Precautions in Handling of Electric Scalpels (Part 2)
16	April 2010	Precautions in Handling of Electric Scalpels (Part 3)
17	May 2010	Precautions in Handling of Prefilled Syringes
18	June 2010	Precautions in Handling of Lancing Devices for Capillary Blood Sampling
19	September 2010	Administration error of concentrated potassium (K) solutions for injection
20	November 2010	Precautions in Artificial Respiration (No.3)
21	January 2011	Precautions in flow rate programming of infusion pumps
22	February 2011	Precautions in Handling Blood Tubing Sets used for Blood Purification
23	April 2011	Precautions in Handling of Insulin Syringes
24	June 2011	Precautions in Using Needle-free Valves
25	September 2011	Precautions for Magnetic Resonance Imaging (MRI) Scans (Part 1)
26	September 2011	Precautions for Magnetic Resonance Imaging (MRI) Scans (Part 2)
27	October, 2011	Precautions in Handling of Drug Products Attached with Reconstitution Solution
28	November, 2011	Precautions in Handling of Blood Glucose Meter
29	December, 2011	Precautions in ECG Monitoring
30	April, 2012	Precautions in Handling of Endotracheal Tubes
31	May, 2012	Precautions in Handling of Radiopharmaceuticals for Injection
32	June, 2012	Precautions in Handling of Closed Suction Catheters
33	September 2012	Accidental Burns during Surgery
34	October 2012	Precautions in Handling of Glycerin Enemas
35	October 2012	Precautions in Handling of Tracheostomy Tubes

3. How to access the "PMDA Medical Safety Information"

The "PMDA Medical Safety Information" is available on the PMDA website. Please utilize it for medical safety activities in medical institutions such as information sharing and training. The "PMDA Medical Safety Information" is sent by e-mail through the "PMDA medi-navi," an e-mail alert service, when it is newly posted on the PMDA website. Healthcare professionals are encouraged to subscribe to the "PMDA medi-navi" to quickly receive the "PMDA Medical Safety Information."

○ PMDA website:
http://www.info.pmda.go.jp/anzen_pmda/iryo_anzen.html (only available in Japanese language)
http://www.pmda.go.jp/english/service/medical_info.html (in English)

○ Subscription to the PMDA medi-navi (only available in Japanese language):
http://www.info.pmda.go.jp/info/idx-push.html

The "PMDA medi-navi" is a free e-mail alert service that promptly provides healthcare professionals with especially important information regarding the safety of drugs and medical devices when it is posted on the PMDA website. ("PMDA medi-navi" is only available in Japanese language.)

4. Closing Comments

New information will be sequentially added to the "PMDA Medical Safety Information" in the future. Healthcare professionals such as safety control managers at medical institutions and other relevant organizations are encouraged to utilize it for promoting the safe use of drugs and medical devices.

In addition to the "PMDA Medical Safety Information," the PMDA website provides other helpful information for ensuring the safe use of drugs and medical devices. Please utilize it and subscribe to the"PMDA medi-navi" to collect information more quickly and actively.

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Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated January 8, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Zanamivir Hydrate

Brand Name (name of company)	RELENZA (GlaxoSmithKline K.K.)
Therapeutic Category	Antivirals
Indications	Treatment of infection of influenza A or B virus and its prevention

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock, anaphylaxis (decreased blood pressure, dyspnoea, pharyngeal oedema, laryngeal oedema, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 7 months (April 1, 2009 to November 5, 2012)

- Allergic shock-associated cases: 3 cases (1 fatal case)

The number of patients using this drug per year estimated by MAHs: approximately 1,700,000 (October 2011 to April 2012)

Launched in Japan: December 2000

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 10s	Influenza (none)	20 mg for 1 day	**Shock** 2 days before administration: The patient started receiving oral administration of tranexamic acid and eprazinone hydrochloride. The patient developed pyrexia and cough in the evening and visited the emergency outpatient department. The patient was diagnosed with influenza and prescribed with zanamivir hydrate on the same day. At this point, the patient had pyrexia of 37.6°C and was instructed to inhale zanamivir hydrate when pyrexia exceeded 38°C. 1 day before administration: The patient did not inhale zanamivir hydrate because her fever did not go higher. Day 1 of administration (day of discontinuation): The patient inhaled zanamivir hydrate (first) due to the increased fever in the morning. Soon after inhaling zanamivir hydrate, the patient had dyspnoea and a feeling of discomfort.

				The patient visited the outpatient pediatric department in the morning and the result of the influenza antigen test was positive for type A. Due to aggravation of cough, the prescription was changed. After that, the patient went home. Her dyspnoea and feeling of discomfort did not improve at home. The patient inhaled the second dose of zanamivir hydrate in the evening (last dose). Her dyspnoea and feeling of discomfort aggravated. Hyperthermia also persisted. Four and a half hours after the second inhalation, the patient visited the emergency outpatient department. When moved to an exam room in six and a half hours after the second inhalation, the patient developed loss of consciousness with facial pallor and impalpable maxillary artery. The doctor performed cardiac massage and the consciousness returned. However, pallor and peripheral coldness were strong. The administration of oxygen was started and intravenous route was secured. The intravenous infusion was started with a 500 mL bottle of physiological saline solution. The pale face improved while receiving the second bottle of intravenous infusion. The patient was admitted to the hospital for detailed examination of the cause and treatment. The fluid replacement, hydrocortisone 200 mg × 1 time, and hydrocortisone 100 mg × 1 time were administered. Inhalation of bronchodilator (salbutamol sulfate) and sodium cromoglicate was performed. 1 day after discontinuation: The fluid replacement and hydrocortisone 100 mg × 2 times were administered. Inhalation of bronchodilator (salbutamol sulfate) and sodium cromoglicate was performed. Due to persistent dyspnoea, the administration of oxygen was continued. Electrocardiographic (ECG) monitoring was continued. 2 days after discontinuation: Dyspnoea significantly improved. 3 days after discontinuation: The administration of oxygen was discontinued and echocardiography showed pericardial effusion. The patient was kept rested on a bed. The administration of hydrocortisone was discontinued. 4 days after discontinuation: The intravenous infusion was discontinued. After receiving a medical examination by the cardiologist of the department of internal medicine, she was instructed to keep resting. 11 days after discontinuation: Disappearance of pericardial effusion was confirmed by echocardiography. 21 days after discontinuation: The patient received a medical examination from a specialist in pediatric cardiology. The general condition was stable, the patient was discharged from the hospital. Follow-up is scheduled a month later. Due to the onset of cardiac arrest, mobility limitation will be carefully lifted. <Test results> Drug lymphocyte stimulation test (DLST): positive (zanamivir hydrate)
	Concomitant medications: antitussives, senega, cherry bark extract, tulobuterol, acetaminophen, tranexamic acid, eprazinone hydrochloride			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 30s	Antiviral prophylaxis (bronchial asthma) (infectious gastroenteritis)	10 mg for 1 day	**Anaphylactic shock** Approximately 8 years before administration: The patient received medication for bronchial asthma (drug name unknown). Approximately 3 years before administration: The therapeutic drug for bronchial asthma was not prescribed. Day 1 of administration: The patient visited a hospital because her family was infected with influenza B virus. The influenza test result for the patient was negative. At the time of her visit, her body temperature was 38.6°C, SpO_2 95, and blood pressure 80/50 mmHg. Due to infectious gastroenteritis, the patient vomited 10 times. 1. Maintenance solution 500 mL + ceftriaxone 2 g 2. Maintenance solution 500 mL 3. Isepamicin sulfate 400 mg (titer) SpO_2 was 99-95 during the intravenous infusions of the above 3 drugs. The patient was able to walk to a restroom and urinate on her own. Zanamivir hydrate was prescribed for prophylaxis of influenza. The patient was in a sitting position after inhaling zanamivir hydrate. About 2 to 3 minutes or several minutes after inhaling zanamivir hydrate, the patient suffered from dyspnoea, rigidity of limbs, eye closure, and impalpable pulse. Resuscitation by administration of epinephrine, cardiac massage, and tracheobronchial intubation were performed, but the patient died after being transferred to another hospital.
	Concomitant medications: non-pyrine common cold drug, levofloxacin hydrate, rebamipide, berberine sulfate hydrate, acetaminophen, maintenance solution, isepamicin sulfate, ceftriaxone sodium hydrate			

2 Josamycin
Josamycin Propionate

Brand Name (name of company)	**Josamycin** Josamycin Tablets 50 mg, 200 mg (Astellas Pharma Inc.) **Josamycin propionate** Josamy Syrup 3%, Josamy Dry Syrup 10% (Astellas Pharma Inc.)
Therapeutic Category	Acting mainly on gram-positive bacteria and mycoplasma
Indications	**Josamycin** <Applicable microorganisms> Josamycin-susceptible strains of *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Shigella*, and *Mycoplasma* <Applicable conditions> Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, secondary infection of trauma injury, thermal burn, and surgical wound, etc., mastitis, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, secondary

	infection of chronic respiratory lesions, cystitis, epididymitis, infectious enteritis, dacryocystitis, hordeolum, otitis media, sinusitis, suppurative sialoadenitis, periodontal inflammation, pericoronitis, maxillary sinusitis, jaw inflammation, scarlet fever **Josamycin propionate** <Applicable microorganisms> Josamycin-susceptible strains of *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Haemophilus influenzae*, and *Mycoplasma* <Applicable conditions> Superficial skin infections, deep-seated skin, chronic pyoderma, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, dacryocystitis, otitis externa, otitis media, sinusitis, periodontal inflammation, maxillary sinusitis, jaw inflammation, scarlet fever

PRECAUTIONS (underlined parts are revised)

Contraindications

Patients with a history of hypersensitivity to ingredients of this drug

Adverse Reactions (clinically significant adverse reactions)

Shock, anaphylaxis: Shock or anaphylaxis may occur. Patients should be carefully monitored, and if abnormalities including urticaria, dyspnoea, and decreased blood pressure are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome): Oculomucocutaneous syndrome may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 6 months (April 1, 2009 to October 25, 2012)

- Shock, anaphylaxis-associated cases: 1 case (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 294,000 (April 2011 to March 2012)

Launched in Japan: June 1970 (tablet)
February 1975 (dry syrup)
October 1981 (syrup)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Dental care (none)	200 mg for 1 day	**Anaphylactic shock** Day 1 of administration (day of discontinuation): The patient visited Hospital A. She did not feel sickness before administration of josamycin. Following dental treatment, the patient took josamycin 200 mg. After that, a symptom (light-headedness) appeared. 6 hours after administration: Numbness lips, redness and itching on the precordial region, abdomen and both upper limbs appeared. A follow-up observation was performed. 7 hours and a half after administration: Because the symptoms did not improve, the patient visited Hospital B and was admitted to the hospital. The patient was able to talk at the time of the visit (Japan

				Coma Scale [JCS]1) and SpO_2 was 95% (Room Air [RA]). After that, SpO_2 gradually decreased to 90%. Blood pressure was 71/25 mmHg. Her level of consciousness gradually decreased and urticaria appeared all over her body. 7 hours and 40 minutes after administration: A route was secured. Epinephrine 0.3 mg was intramuscularly administered. d-chlorpheniramine 5 mg and famotidine 20 mg were intravenously administered. Blood pressure was improved to 102/55 mmHg, but whole body tremulousness appeared. 8 hours and a half after administration: Methylprednisolone 125 mg was intravenously administered. Tremulousness disappeared with disappearance of dyspnoea. 1 day after discontinuation: The symptoms remitted and the patient was discharged from the hospital.
	Concomitant medications: aspirin, atenolol, rosuvastatin calcium, sodium rabeprazole, alprazolam, sodium hyaluronate			

Laboratory Examination

	Day 1 of administration	7 hours and a half after administration	7 hours and 40 minutes after administration
WBC (/mm^3)	5300	-	-
Neutrophils (%)	58.1	-	-
Eosinophils (%)	1.1	-	-
Basophils (%)	0.7	-	-
Monocytes (%)	6.2	-	-
Lymphocytes (%)	33.9	-	-
LDH (IU/L)	190	-	-
CK (CPK) (IU/L)	177	-	-
BUN (mg/dL)	15	-	-
Creatinine (mg/dL)	0.7	-	-
CRP (mg/dL)	0.032	-	-
Systolic blood pressure (mmHg)	-	71	102
Diastolic blood pressure (mmHg)	-	25	55

3 Sunitinib Malate

Brand Name (name of company)	SUTENT Capsule 12.5 mg (Pfizer Japan Inc.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Imatinib-resistant gastrointestinal stromal tumours Radically unresectable or metastatic renal cell carcinoma Pancreatic neuroendocrine tumour

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Oculomucocutaneous syndrome or erythema multiforme may occur. The patient should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years and 8 months (April 1, 2009 to December 1, 2012)

- Oculomucocutaneous syndrome: 1 case (no fatal cases)
- Erythema multiforme: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 2,100 (April 2011 to March 2012)

Launched in Japan: June 2008

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Renal cell carcinoma (colon cancer, metastases to lymph node)	37.5 mg for 12 days	**Stevens-Johnson syndrome** <History of prior treatment> Surgery: radical nephrectomy of the right kidney, sigmoidectomy 5 days before administration: The patient was admitted to the hospital for the treatment with sunitinib malate. 1 day before administration: Performance status (PS) was 1. Day 1 of administration: The administration of sunitinib malate 37.5 mg/day was started for the treatment of renal cell carcinoma. Day 12 of administration (day of discontinuation): The patient complained of generalised itching in the morning. In the evening, the patient's state of consciousness decreased and he could not speak well (dysarthria). The patient had urinary incontinence and he could not walk (gait disturbance). Administration of sunitinib malate was discontinued. 1 day after discontinuation: In the morning, redness appeared on the chest/abdomen, back, upper arm, corners of the mouth and jaw. The patient also developed eye discharge and oral pain. About 2 hours and 30 minutes later, his body temperature increased to 38°C. The patient visited the department of dermatology in the evening. The patient was diagnosed with suspected Stevens-Johnson syndrome (SJS) and a skin biopsy of his left upper arm was performed. Brain computed tomography (CT) did not show haemorrhage/infarction, while magnetic resonance imaging (MRI) only showed age-related changes. The patient also was visited by an ophthalmologist and was prescribed with ophthalmic medication. Administration of methylprednisolone sodium succinate 1000 mg/day was started. [Skin symptoms at the time of diagnosis] Characteristic of skin eruption: red, punctate to macular, strong on the trunk and mild on extremities, bulbar conjunctiva (redness, eye discharge), perioral erosion, oral mucosa redness Blistering: no Enanthema: yes (oral mucosa redness, conjunctival hyperaemia) Symptom: yes (itchy skin) 2 days after discontinuation:

				Both rash and incontinence persisted and the patient was unable to articulate properly. 3 days after discontinuation: Administration of methylprednisolone sodium succinate was discontinued. 4 days after discontinuation: Rash did not become aggravated. Administration of betamethasone sodium phosphate 30 mg/day was started. 5 days after discontinuation: Rash was alleviated. 7 days after discontinuation: The dose of betamethasone sodium phosphate was reduced to 20 mg/day. 8 days after discontinuation: Administration of betamethasone sodium phosphate was discontinued. 9 days after discontinuation: The pathological findings were consistent with the symptoms of SJS. Administration of prednisolone sodium succinate 30 mg/day was started. 12 days after discontinuation: Dysarthria persisted. The dose of prednisolone sodium succinate was reduced to 20 mg/day. 15 days after discontinuation: The patient visited the department of neuropsychiatry. The patient was diagnosed with dementia, not with Parkinson's disease. The dose of prednisolone sodium succinate was reduced to 10 mg/day. 17 days after discontinuation: Administration of prednisolone sodium succinate was discontinued. 18 days after discontinuation: Skin eruptions were observed only with subcutaneous bleeding spots in the central areas and the other region resolved. It was considered that SJS was cured. Dysarthria and gait disturbance were alleviated but persisted. 19 days after discontinuation: The patient recovered from SJS. 28 days after discontinuation: The patient visited the department of neurology at a nearby hospital. He was diagnosed that dysarthria was caused by reduced general condition and mild cerebrovascular dementia, while it is highly possible that gait disturbance was caused by disuse syndrome. 42 days after discontinuation: Although there were mild dysarthria and gait disturbance, the patient recovered enough to be discharged from the hospital.
	Concomitant medications: sennoside, sodium bicarbonate/monobasic sodium phosphate anhydrous			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Renal cell carcinoma (metastases to lung, metastases to brain)	37.5 mg for 16 days	**Erythema multiforme** <History of prior treatment> Surgery: nephrectomy, tumourectomy in neurocranium History of radiotherapy: brain (gamma knife) Medications: sorafenib tosilate 1 day before administration:The patient' PS was 1. Platelet count

				was 79000/μL. Day 1 of administration: The administration of sunitinib malate 37.5 mg/day was started for the treatment of renal cell carcinoma. Day 15 of administration: Erythema multiforme and decreased platelets (Grade 3) developed, prolongation of the hospitalisation period was required. [Skin symptoms at the time of diagnosis] Characteristic of skin eruption: redness, wheals, generalised Blistering: no Enanthema: no Subjective symptom: yes (itching) Day 16 of administration (day of discontinuation): Administration of sunitinib malate was discontinued. 2 days after discontinuation: Administration of topical corticosteroid was started. 19 days after discontinuation: Erythema multiforme disappeared. Platelet count resolved to 63000/μL (Grade 2).
	Concomitant medications: sodium valproate, famotidine, magnesium oxide, tamsulosin hydrochloride, goreisan			

4 **Ryutanshakanto** (for Ethical Use)

Brand Name (name of company)	TSUMURA Ryutanshakanto Extract Granules for Ethical Use (Tsumura & Co.) Kotaro Ryutanshakanto Extract Fine Granule (Kotaro Pharmaceutical Co., Ltd.) JUNKOU Ryutanshakanto Extract Fine Granules for Ethical Use (Kowa Yakutsu Co., Ltd.) SANWA Ryutanshakanto Extract Fine Granules (Sanwa Shoyaku Co., Ltd.) Taikodo Ryutanshakanto Extract Fine Granule, Taikodo Ryutanshakanto Extract Powder, Taikodo Ryutanshakanto Extract Granule (Taikoseido Pharmaceutical Co., Ltd.)
Therapeutic Category	Kampo product
Indications	Following symptoms of those patients with a comparatively strong constitution whose muscles in the lower abdomen are likely to become tense: painful micturition, feeling of residual urine, turbid urine, and leukorrhea

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: If cough, dyspnoea, pyrexia, or abnormal chest sounds are observed, administration of this drug should be discontinued, examinations including chest X-ray and chest CT scan should be performed immediately, 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) for the past 3 years and 7 months (April 1, 2009 to November 15, 2012)

- Interstitial pneumonia-associated cases: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 15,400 (April 2011 to March 2012)

Launched in Japan: October 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Prostatic hyperplasia (hepatic cirrhosis B, hypertension, irritable bowel syndrome, reflux oesophagitis)	7.5 g for 48 days	Interstitial pneumonia Day 1 of administration: The patients started receiving ryutanshakanto for the treatment of prostatic hyperplasia. Approximately 1 month after administration: The patient noticed common cold-like symptoms and exertional dyspnoea. Day 47 of administration: Though the symptoms were mild, because SpO_2 at resting had decreased to 80% in the routine examination by a primary physician and CT scans showed ground-glass opacities in both lungs, the patient was admitted to the hospital. Day 48 of administration (day of discontinuation): The patient was transferred to this hospital and administration of ryutanshakanto was discontinued. Antinuclear antibody (negative), anti-Sjögren's syndrome A/Ro (SS-A/Ro) (negative), anti-Sjögren's syndrome B/La (SS-B/La) (negative) 1 day after discontinuation: The respiratory condition did not improve, steroid therapy was started. DLST was submitted prior to the administration of steroids. After that, the C-reactive protein (CRP) level and the necessary amount of oxygen decreased. Because imaging test showed ground-glass opacities with improving, the dose of steroids was reduced. DLST: Ryutanshakanto (positive) 13 days after discontinuation: Since CT scans showed that interstitial shadows were disappearing, the patient was withdrawn from oxygen inhalation.
	Concomitant medications: chimaphila umbellata ext/populus tremula ext./pulsatilla pratensis mill ext./equisetum arvense ext./purified wheat germ oil, ursodeoxycholic acid, L-isoleucine/L-leucine/L-valine, clostridium butyricum (miyairi) powder, lansoprazole, telmisartan, spironolactone			

Clinical Symptoms

	Day 1 of administration	Day 47 of administration	Day 48 of administration (day of discontinuation)	3 days after discontinuation
Pyrexia	No	No	No	No
Sputum	No	No	No	No
Cough	No	Mild	Mild	No
Shortness of breath (HJ classification)	I	II	V	IV

Laboratory Examination

	Approx. 1 month before administration	Day 48 of administration (day of discontinuation)	2 days after discontinuation	5 days after discontinuation	12 days after discontinuation
LDH (IU/L)	157	319	262	216	154
CRP (mg/dL)	0.17	5.61	6.34	0.53	0.53
KL-6 (U/mL)	-	848	783	859	787

3

Revision of Precautions (No. 243)

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 January 8, 2013 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1

Antidiabetic agents

Glimepiride
Pioglitazone Hydrochloride/Glimepiride

Brand Name	Amaryl 0.5 mg Tablets, Amaryl 1 mg Tablets, Amaryl 3 mg Tablets (Sanofi K.K.) and the others SONIAS Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
Adverse Reactions (clinically significant adverse reactions)	**Pancytopenia, agranulocytosis, haemolytic anaemia, decreased platelets**: Pancytopenia, agranulocytosis, haemolytic anaemia, and decreased platelets may occur. Patients should be carefully monitored and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

2

Acting mainly on gram-positive and gram-negative bacteria

Cefozopran Hydrochloride

Brand Name	FIRSTCIN INTRAVENOUS 0.5 Gm., 1 Gm., FIRSTCIN INTRAVENOUS 1 Gm. BAG S, FIRSTCIN INTRAVENOUS 1 Gm. BAG G (Takeda Pharmaceutical Company Limited)
Adverse Reactions (clinically significant adverse reactions)	Pancytopenia, agranulocytosis, granulocytopenia, and decreased platelets may occur. Haemolytic anaemia associated with other cephem antibiotics have been reported. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

3

Acting mainly on gram-positive and gram-negative bacteria

Cefotiam Hydrochloride

Brand Name	PANSPORIN INTRAVENOUS 0.25 Gm., 0.5 Gm., 1 Gm., PANSPORIN INTRAVENOUS 1 Gm. Bag S, PANSPORIN INTRAVENOUS 1 Gm. Bag G (Takeda Pharmaceutical Company Limited), Halospor for Intravenous Injection 0.25 g, 0.5 g, 1 g (Toyama Chemical Company Limited)
Adverse Reactions (clinically significant adverse reactions)	**Pancytopenia, agranulocytosis, granulocytopenia, haemolytic anaemia, decreased platelets**: Pancytopenia, agranulocytosis, granulocytopenia, haemolytic anaemia, and decreased platelets may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

4

Antivirals

Atazanavir Sulfate
Abacavir Sulfate
Indinavir Sulfate Ethanolate
Etravirine
Efavirenz
Emtricitabine
Emtricitabine/Tenofovir Disoproxil Fumarate
Saquinavir Mesilate
Sanilvudine
Didanosine
Zidovudine
Zidovudine/Lamivudine
Darunavir Ethanolate
Tenofovir Disoproxil Fumarate
Nevirapine
Nelfinavir Mesilate
Fosamprenavir Calcium Hydrate
Maraviroc
Lamivudine (150 mg, 300 mg)
Lamivudine/Abacavir Sulfate
Raltegravir Potassium
Ritonavir
Rilpivirine Hydrochloride
Lopinavir/Ritonavir

Brand Name

REYATAZ CAPSULES 150 mg, 200 mg (Bristol-Myers K.K.)
Ziagen Tablets 300 mg (ViiV Healthcare K.K.)
CRIXIVAN Capsules 200 mg (MSD K.K.)
INTELENCE Tablets 100 mg (Janssen Pharmaceutical K.K.)
STOCRIN Tablets 200 mg, 600 mg (MSD K.K.)
Emtriva Capsules 200 mg (Japan Tobacco Inc.)
Truvada Combination Tab. (Japan Tobacco Inc.)
INVIRASE Capsule 200 mg, INVIRASE Tablet 500 mg (Chugai Pharmaceutical Co., Ltd.)
ZERIT CAPSULES 15, 20 (Bristol-Myers K.K.)
VIDEX EC CAPSULES Enteric-Coated Beadlets 125, 200 (Bristol-Myers K.K.)
Retrovir Capsules 100 mg (ViiV Healthcare K.K.)
Combivir Combination Tablets (ViiV Healthcare K.K.)
PREZISTA Tablets 300 mg, PREZISTANAIVE Tablets 400 mg (Janssen Pharmaceutical K.K.)
Viread Tab. 300 mg (Japan Tobacco Inc.)

Viramune Tablets 200 (Nippon Boehringer Ingelheim Co., Ltd.)
Viracept Tab. 250 mg (Japan Tobacco Inc.)
Lexiva Tablets 700 (ViiV Healthcare K.K.)
CELSENTRI Tablets 150 mg (ViiV Healthcare K.K.)
Epivir Tablets 150, 300 (ViiV Healthcare K.K.)
Epzicom Combination Tablets (ViiV Healthcare K.K.)
ISENTRESS Tablets 400 mg (MSD K.K.)
Norvir Tablets 100 mg, Norvir Oral Solution 8% (Abbott Japan Co., Ltd.)
EDURANT Tablets 25 mg (Janssen Pharmaceutical K.K.)
Kaletra Combination Tablets, Kaletra Combination Oral Solution (Abbott Japan Co., Ltd.)

Important Precautions

Immune reconstitution syndrome has been reported in patients treated with multidrug therapy of anti-HIV drugs including this drug. After the start of administration of this drug, immune function improves and an inflammatory reaction to not only symptomatic but also asymptomatic opportunistic infection (caused by mycobacterium avium complex, cytomegalovirus, pneumocystis, etc.) may occur. Autoimmune diseases (e.g., hyperthyroidism, polymyositis, Guillain-Barre syndrome, uveitis) have been reported associated with the improvement of immune function, these symptoms should be assessed and appropriate treatment should be considered when necessary.

5

Over-the-counter drugs

Ryutanshakanto

Brand Name

Ryutanshakanto Extract Tablet Kracie (Kracie Pharma, 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.
Interstitial pneumonia: Shortness of breath or difficulty in breathing when climbing the stairs or during light exertion, dry cough, pyrexia, etc. may occur suddenly or persist.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of new drugs. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for 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 adverse drug reactions. EPPV is specified as a condition of approval.

(As of February 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Sodium Phenylbutyrate Buphenyl Tablets 500 mg, Buphenyl Granules 94%	Orphan Pacific, Inc.	January 17, 2013
Lanreotide Acetate Somatuline 60 mg for s.c. Injection, Somatuline 90 mg for s.c. Injection, Somatuline 120 mg for s.c. Injection	Teijin Pharma Limited.	January 17, 2013
Omega-3-acid ethyl esters 90 LOTRIGA Granular Capsule 2 g	Takeda Pharmaceutical Company Limited	January 10, 2013
Carmustine Gliadel 7.7 mg Implant	Nobelpharma Co., Ltd.	January 9, 2013
Tobramycin TOBI Inhalation solution 300 mg	Novartis Pharma K.K.	January 9, 2013
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*[1]	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012
Irbesartan/Amlodipine Besilate AIMIX Combination Tablet LD, HD	Dainippon Sumitomo Pharma Co., Ltd.	December 19, 2012
Olanzapine Zyprexa Rapid Acting Intra-Muscular Injection 10 mg	Eli Lilly Japan K.K.	December 3, 2012
Anagliptin SUINY Tab. 100 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	November 30, 2012
Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL	Bayer Yakuhin, Ltd.	November 27, 2012
Stiripentol DIACOMIT DRYSYRUP 250 mg, 500 mg, DIACOMIT CAPSULES 250 mg	Meiji Seika Pharma Co., Ltd	November 27, 2012
Glycopyrronium Bromide seebri inhalation capsules 50 μg	Novartis Pharma K.K.	November 22, 2012
Tigecycline Tygacil Injection 50 mg	Pfizer Japan Inc.	November 22, 2012
Lubiprostone Amitiza Capsules 24 μg	Sucampo Pharma Ltd.	November 22, 2012

Botulinum Toxin Type A BOTOX for injection 50 Unit, 100Unit*2	GlaxoSmithKline K.K.	November 21, 2012
Everolimus AFINITOR tablets 5 mg, 2.5 mg*3	Novartis Pharma K.K.	November 21, 2012
Triamcinolone Acetonide MaQaid intravitreal injection 40 mg*4	Wakamoto Co., Ltd.	November 21, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine TETRABIK Subcutaneous Injection Syringe	The Research Foundation for Microbial Diseases of Osaka University	October 31, 2012
Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine Quattrovac Subcutaneous Injection Syringe	The Chemo-Sero-Therapeutic Research Institute	October 31, 2012
Degarelix Acetate Gonax 80 mg for Subcutaneous Injection, Gonax 120 mg for Subcutaneous Injection	Astellas Pharma. Inc.	October 23, 2012
Clopidogrel Sulfate PLAVIX 25 mg Tablets, 75 mg Tablets*5	Sanofi-aventis K.K.	September 28, 2012
Tazobactam Sodium/Piperacillin Sodium ZOSYN for Intravenous Injection 2.25, 4.5*6	Taiho Pharmaceutical Co., Ltd.	September 28, 2012
Pazopanib Hydrochloride Votrient Tablets 200 mg	GlaxoSmithKline K.K.	September 28, 2012
Iguratimod KOLBET Tablets 25 mg	Toyama Chemical Co., Ltd.	September 12, 2012
Iguratimod Careram Tablets 25 mg	Eisai Co., Ltd.	September 12, 2012
Teneligliptin Hydrobromide Hydrate TENELIA Tablets 20 mg	Mitsubishi Tanabe Pharma Corporation	September 10, 2012
Formoterol Fumarate Hydrate Oxis 9 μg Turbuhaler 28 doses, 60 doses*7	AstraZeneca K.K.	September 3, 2012
Inactivated Poliomyelitis Vaccine (Salk Vaccine) IMOVAX POLIO subcutaneous	Sanofi Pasteur K.K.	August 31, 2012
Axitinib Inlyta Tablets 1 mg, 5 mg	Pfizer Japan Inc.	August 30, 2012
Ropinirole Hydrochloride ReQuip CR Tablets 2 mg, 8 mg	GlaxoSmithKline K.K.	August 28, 2012
Atomoxetine Hydrochloride Strattera Capsule 5 mg, 10 mg, 25 mg, 40 mg*8	Eli Lilly Japan K.K.	August 24, 2012
Sulbactam Sodium/Ampicillin Sodium UNASYN-S for Intravenous Use 0.75 g, 1.5 g, UNASYN-S KIT for Intravenous Use 1.5 g, 3 g*9, 10	Pfizer Japan Inc.	August 10, 2012
Budesonide/Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses*11	AstraZeneca K.K.	August 10, 2012
Perflubutane SONAZOID FOR INJECTION 16 μL*12	Daiichi Sankyo Company, Limited	August 10, 2012
Sunitinib SUTENT Capsule 12.5 mg*13	Pfizer Japan Inc.	August 10, 2012

*1 An additional indication for "treatment of patients with central diabetes insipidus"

*2 An additional indication for "treatment of patients with severe primary axillary hyperhidrosis"

*3 An additional indication for “treatment of patients with renal angiomyolipoma associated with tuberous sclerosis, subependymal giant cell astrocytoma associated with tuberous sclerosis”

*4 An additional indication for “treatment of patients with diabetic macular oedema”

*5 An additional indication for “prevention of thrombus and embolus formation in patients with peripheral arterial disease”

*6 An additional indication for “treatment of patients with peritonitis, intra-abdominal abscess, cholecystitis, or cholangitis”

*7 An additional indication for “remission of various symptoms associated with airway obstructive disorder in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)”

*8 An additional indication for “treatment of patients with attention deficit/hyperactivity disorder (AD/HD) in adulthood”

*9 An additional indication for “Streptococcus pneumonia, Moraxella (Branhamella) catarrhalis”

*10 An additional administration for “severe infections”

*11 An additional indication for “remission of various symptoms in patients with chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 agonist)”

*12 An additional indication for “contrast enhanced imaging for breast mass lesion in mammary ultrasonography”

*13 An additional indication for “treatment of patients with pancreatic neuroendocrine tumour”

Adverse Drug Reaction Term “Anaphylaxis”

1. Introduction

Package inserts are intended to provide healthcare professionals with appropriate information based on the latest evidence. An adverse drug reaction term, “anaphylactoid symptoms,” which has been used in package inserts, will be changed to “anaphylaxis” based on recent evidence.

2. Background

The main onset mechanism of anaphylaxis is the immediate (type I) IgE-mediated allergic reaction. In actual clinical cases, however, IgE is often not measured when the diagnosis is made, so whether it is IgE-mediated or non-IgE-mediated anaphylaxis cannot always be determined. Based on this, the term “anaphylactoid symptoms” has been used as a term that includes both cases.

In recent years, however, use of the term “anaphylaxis”, regardless of IgE involvement, has been becoming mainstream according to guidelines such as the “Manuals for Management of Individual Serious Adverse Drug Reactions” prepared by MHLW with collaboration of academic societies and the suggestion by the World Allergy Organization (hereinafter referred to as the “WAO”). In response to this, MHLW/PMDA has examined the necessity of the change of the term used in package inserts.

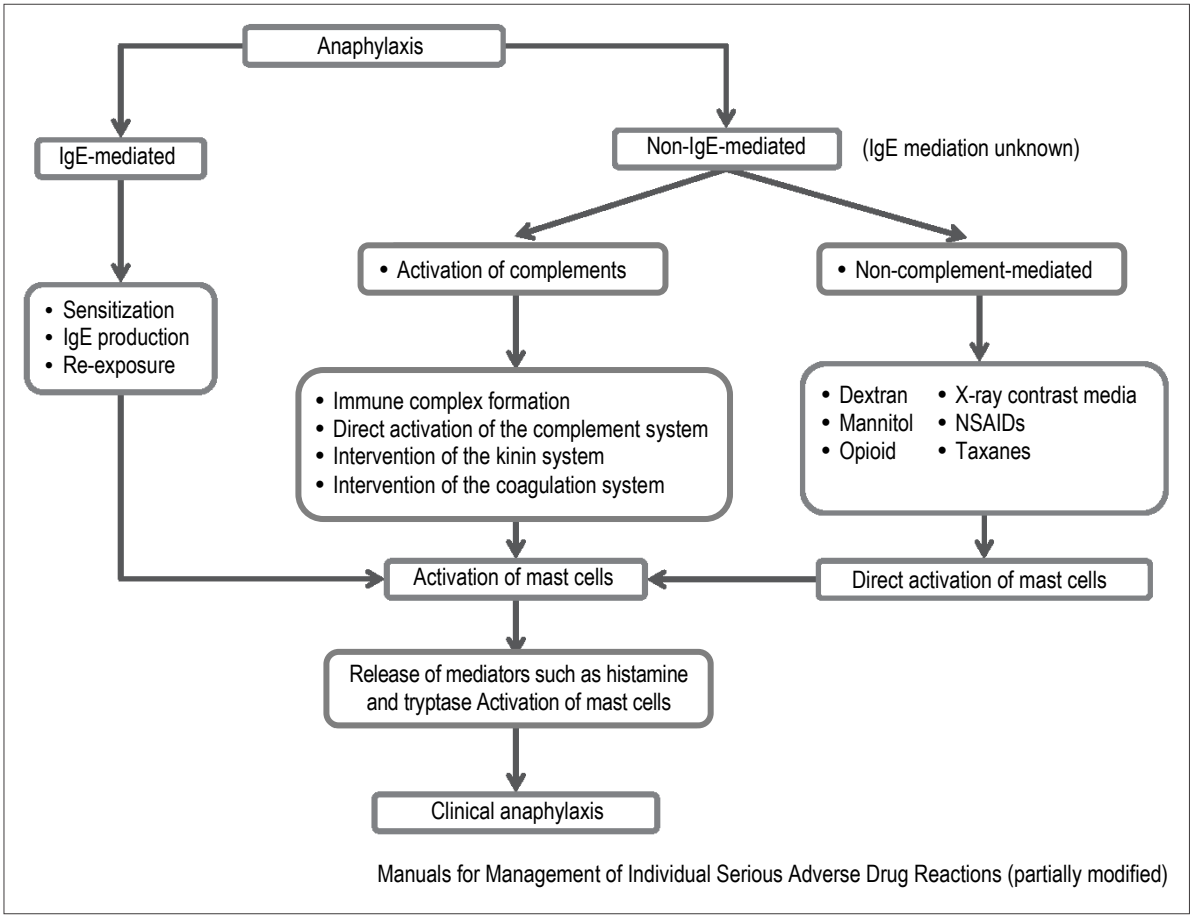
3. Classification of anaphylaxis (cited from the Manuals for Management of Individual Serious Adverse Drug Reactions)

The main onset mechanism of anaphylaxis is the immediate (type I) allergic reaction. In general, after sensitization to a drug (allergen), when a sensitized individual is exposed to the same allergen, the allergen and IgE antibody on the surface of mast cells or basophils cause an antigen-antibody reaction, which triggers the release of chemical mediators such as histamine, tryptase, bradykinin or cysteinyl leukotriene from these cells, thereby inducing various symptoms.

There is also a mechanism of hypersensitivity which is not mediated by IgE. When the complement system is activated by immune complex or other stimuli, anaphylatoxins, such as C3a and C5a, are produced. They can be fixed on the surface of mast cells and trigger the release of chemical mediators from mast cells without involvement of high-affinity IgE receptors. In addition to the above mechanisms, drugs such as hypertonic solutions including mannitol can stimulate the release of mediators from mast cells through an unknown mechanism without involvement of IgE or complements. The mechanism is considered to be associated with the activation of macrophages by IgG class antibodies and the release of platelet-activating factors. Opioid has been also assumed to directly act on mast cells. For nonsteroidal antiinflammatory drugs (NSAIDs), their original action mechanism may increase the overprodcution of cysteinyl leukotriene[1)].

The above conditions are referred to as anaphylaxis regardless of IgE involvement (**Figure 1**).

Figure 1 Classification by mechanism of anaphylaxis



4. The WAO's Definition of anaphylaxis

The WAO proposes a broad definition of "anaphylaxis" as follows: "Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction." and suggests that the term "anaphylactoid" should not be used[2, 3]. In addition, the WAO recommends that the term "allergic anaphylaxis" should be used for reactions based on immunologic mechanisms mediated by IgE, IgG, or immune complexes, and for all reactions other than "allergic anaphylaxis," the term "nonallergic anaphylaxis" should be used.

5. Future actions

"Anaphylaxis" used in package inserts is to be defined as "a severe, life-threatening, generalized or systemic hypersensitivity reaction" proposed by the WAO. For such reaction, the adverse drug reaction term "anaphylaxis" will be used in package inserts regardless of its mechanism. Additional information on mechanism (e.g., a reaction mediated by immune complexes) may be included if it should be noted.

<References>

1) MHLW: Manuals for Management of Individual Serious Adverse Drug Reactions "Anaphylaxis" (2008) http://www.info.pmda.go.jp/juutoku/file/jfm0803003.pdf (only available in Japanese language)
2) Johansson et al.: Position paper; A revised nomenclature for allergy An EAACI position statement from the EAACI nomenclature task force. Allergy 56: 813–824 (2001)
3) Johansson et al.: Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 113: 832–836 (2004)