Pharmaceuticals and Medical Devices Safety Information

No. 293 August 2012

Table of Contents

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. 293 August 2012

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)
cpm	counts per minute
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
DNA	Deoxyribonucleic acid
eGFR	Estimated glomerular filtration rate
EBV	Epstein-Barr virus
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HPS	Haemophagocytic syndrome
ICU	Intensive care unit
IU	International unit
MAH	Marketing authorization holder
MRSA	Methicillin-resistant Staphylococcus aureus
OTC	Over-the-counter drug
PAL	Pharmaceutical Affairs Law
RBC	Red blood cell count
S.I.	Stimulation index
SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
WBC	White blood cell count

1

Serious Adverse Reactions Associated with Over-the-counter Drugs

1. Introduction

Adverse drug reactions are reported to the MHLW through marketing authorization holders (MAHs) or directly from healthcare professionals in accordance with the Pharmaceutical Affairs Law (PAL). Such reported adverse reactions include some serious adverse reactions resulting from the use of over-the-counter (OTC) drugs, and therefore attention to adverse reactions associated with OTC drugs is also required.

Reports of serious adverse reactions associated with OTC drugs submitted by MAHs from 2007 to 2011 are presented below.

2. Adverse Reaction Reporting System according to the Pharmaceutical Affairs Law

When MAHs of drugs or medical devices find adverse reactions, infections associated with drugs or medical devices, medical device defects, or become aware of occurrence of them from a research report etc., it is mandatory for the MAHs to report them to the Minister of Health, Labour and Welfare as stipulated in Article 77, 4-2, Paragraph 1 of the PAL. In addition, for healthcare professionals such as physicians, dentists, and pharmacists, it is also mandatory to report adverse reactions associated with drugs or medical devices, or medical device defects directly to the Minister of Health, Labour and Welfare as stipulated in Article 77, 4-2, Paragraph 2 of the PAL, provided that such reporting is deemed necessary to prevent occurrence or spread of public health hazards. Information on health hazards (adverse reactions, infections, and medical device defects) resulting from use of drugs or medical devices, which are reported according to the above provisions, is analyzed and evaluated from experts' point of view at PMDA. Based on the results of the analysis and evaluation, MHLW determines necessary safety measures, provides necessary information to a wide range of healthcare professionals, and implements post-marketing safety measures for associated drugs and medical devices.

3. Reports of adverse reactions suspected of being caused by OTC drugs (from 2007 to 2011)

A total of 1220 reports of adverse reaction associated with OTC drugs were submitted by MAHs for 5 years from FY 2007 to FY 2011: approximately 250 cases were reported annually (Figure 1). The number of reported adverse reactions by therapeutic category is 404 cases for common cold drugs, 243 cases for antipyretics, analgesics and anti-inflammatory agents, and 132 cases for Kampo medicines (Table 1). Of these adverse reactions, there are 24 fatal cases in total; according to therapeutic category, 12 cases for common cold drugs, 4 cases for antipyretics, analgesics and anti-inflammatory agents, and 2 cases for Kampo medicines, etc. (Table 2). A total of 15 cases are associated with sequelae; according to therapeutic category, 8 cases for common cold drugs, 2 cases for antipyretics, analgesics and anti-inflammatory agents, and 2 cases for calcium preparations, etc. (Table 3). Serious or fatal adverse reactions including anaphylactic shock, hepatic dysfunction, and Stevens-Johnson syndrome have been also reported for OTC drugs, as shown in the following tables.

Figure 1. Annual number of adverse reaction reports associated with OTC drugs

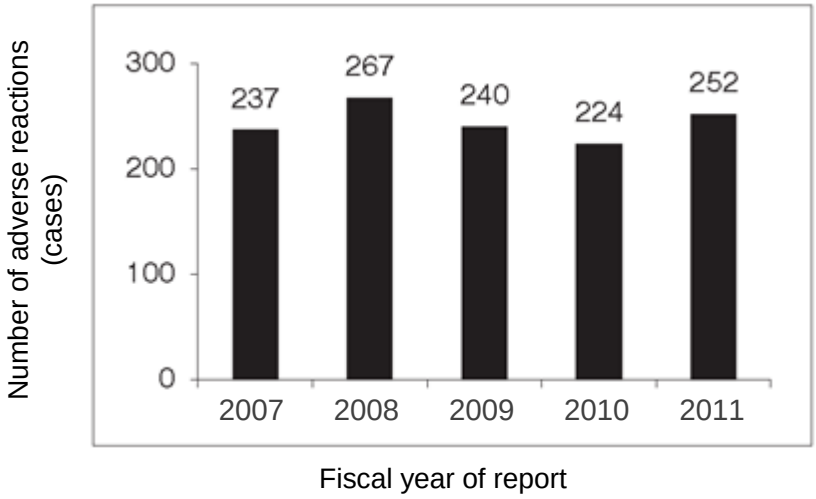

Table 1 Adverse reactions by therapeutic category (from FY 2007 to FY 2011)[1, 2)]

Therapeutic category	Cases of adverse reactions	Major adverse reactions
Common cold drugs (cold remedies)	404	Stevens-Johnson syndrome, interstitial lung disease, fulminant hepatitis, etc.
Antipyretics, analgesics, and anti-inflammatory agents	243	Stevens-Johnson syndrome, status asthmaticus, renal disorder, etc.
Kampo medicines	132	Hepatic function abnormal, interstitial lung disease, pseudoaldosteronism, etc.
Smoking cessation aids	70	Anaphylactoid reaction, angina pectoris, depression, etc.
Otic and nasal agents	47	Rhabdomyolysis, convulsion, dyspnoea, etc.
Antitussives and expectorants	25	Anaphylactic shock, toxic skin eruption, jaundice, etc.
Analgesics, anti-itchings, astringents, anti-inflammatory agents	24	Dermatitis contact, anaphylactic shock, generalised erythema, etc.
Crude drugs and Kampo medicines-Miscellaneous	24	Hepatic function disorder, pseudoaldosteronism, interstitial lung disease, etc.
Calcium preparations	23	Colonic polyp, cholelithiasis, cataract, etc.
Others	228	-
Total	1220	

1 The adverse reactions were reported by MAHs and include those with unknown causality to the drug.
2 Data are presented as summary values as of the end of April 2012.

Table 2 Fatal cases (from FY 2007 to FY 2011)[3, 4)]

Therapeutic category	Cases of adverse reactions	Major adverse reactions
Common cold drugs (cold remedies)	12	Toxic epidermal necrolysis, liver disorder, interstitial lung disease, Stevens-Johnson syndrome, etc.
Antipyretics , analgesics and anti-inflammatory agents	4	Reye's syndrome, status asthmaticus, metabolic acidosis, etc.
Kampo medicines	2	Interstitial lung disease
Antacids	1	Toxic epidermal necrolysis
Hypnotics and sedatives, anxiolytics	1	Death
Antitussives and expectorants	1	Altered state of consciousness, ventricular tachycardia
Multivitamin preparations (Except for combination products of vitamin A and D)	1	Fulminant hepatitis
Metabolic disease preparations & combinations	1	Drug-induced liver injury
Allergic agents-Miscellaneous	1	Exophthalmos, eye pain, vomiting
Total	24	

Table 3 Cases with sequelae (from FY 2007 to FY 2011)[5, 6)]

Therapeutic category	Cases of adverse reactions	Major adverse reactions
Common cold drugs (cold remedies)	8	Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.
Antipyretics , analgesics and anti-inflammatory agents	2	Oculomucocutaneous syndrome, cerebellar ataxia
Calcium preparations	2	Retinal detachment, alveolar osteitis
Antitussives and expectorants	1	Stevens-Johnson syndrome
Gastrointestinal agents and combinations	1	Glomerulonephritis
Vitamins-Miscellaneous	1	Pulmonary embolism
Total	15	

[3] These fatal cases were reported by MAHs and include those with unknown causality between the adverse reactions and death.
[4] Data are presented as summary values as of the end of April 2012.
[5] The cases with sequelae were reported by MAHs and include those with unknown causality between the adverse reactions and sequelae.
[6] Data are presented as summary values as of the end of April 2012.

4. Closing comments

Serious adverse reactions have been also reported for OTC drugs, which includes fatal cases and cases with sequelae. In general, early detection of adverse reactions is important to prevent aggravation of related symptoms; however, adverse reactions to OTC drugs are less recognized, and their detection may therefore be delayed compared to adverse reactions to ethical drugs. When providing OTC drugs, pharmacists or registered salespersons are encouraged to inform users of initial symptoms of adverse reactions, depending on the type of drug, to promote detection of initial symptoms by users themselves. Pharmacists or registered salespersons are also encouraged to instruct users to seek medical aid or consult pharmacists, etc. at a pharmacy or drug store, if they become aware of any of these initial symptoms. When consulted by users, healthcare professionals should check initial symptoms so that adverse reactions can be detected early.

MHLW prepared "Manuals for Management of Individual Serious Adverse Drug Reactions" posted on the websites of MHLW and PMDA, which summarizes the initial symptoms, clinical courses and treatments of serious adverse reactions. This manual should be utilized.

The "PMDA medi-navi" is a mail delivery service provided by PMDA free of charge (see PMDSI No. 278 and No. 289 for details), which also delivers information on revision of package inserts of OTC drugs. When providing medical care, healthcare professionals are encouraged to make use of updated information in the PMDA medi-navi as well as information posted on the PMDA's website.

Health hazards that require treatment equivalent to inpatient care due to an adverse reaction despite proper use of a drug may be covered by the Relief System for Sufferers from Adverse Drug Reactions (see PMDSI No. 262, No. 273, and No. 286 for details). Adverse reactions associated with OTC drugs are also covered by the system. Therefore, when an adverse reaction associated with an OTC drug occurs, or when a consultation is given about such an adverse reaction, and in addition when this health hazard seems to be applicable to the relief benefit, healthcare professionals are encouraged to introduce the system to users and prepare a medical certificate, a proof of purchase, etc.

- Manuals for Management of Individual Serious Adverse Drug Reactions
  http://www.info.pmda.go.jp/juutoku/juutoku_index.html (only available in Japanese language)
- PMDA medi-navi page
  http://www.info.pmda.go.jp/info/idx-push.html (only available in Japanese language)
- Contact information for the Relief System for Sufferers from Adverse Drug Reactions
  Pharmaceuticals and Medical Devices Agency
  (Relief System Consultation Service)
  Operating hours:
  [Monday to Friday] 9:00-17:00 (excluding national holidays and New Year holidays)
  Email: kyufu@pmda.go.jp
  Website: http://www.pmda.go.jp/kenkouhigai.html (only available in Japanese language)

2

Important Safety Information

Regarding the revision of the Precautions sections of package inserts of drugs in accordance with the Notification dated July 10, 2012, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Pregabalin

Brand Name (name of company)	LYRICA Capsules 25 mg, 75 mg, 150 mg (Pfizer Japan Inc.)
Therapeutic Category	Central nervous system agents-Miscellaneous
Indications	Peripheral neuropathic pain, pain associated with fibromyalgia

PRECAUTIONS (underlined parts are revised)

Important Precautions

Some cases of dizziness, somnolence, loss of consciousness, etc. leading to automobile accidents have been reported after administration of this drug. Patients treated with this drug should be advised to refrain from engaging in potentially hazardous machine operations including driving. Especially in elderly patients, some cases of fall resulting in fracture due to any of these symptoms occurred, and therefore extra caution should be exercised.

Adverse Reactions (clinically significant adverse reactions)

Dizziness, somnolence, loss of consciousness: Some cases of dizziness, somnolence, or loss of consciousness leading to fall and then fracture have been reported. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration or dose reduction should be taken.

Hypoglycaemia: Hypoglycaemia may occur. If symptoms of hypoglycaemia such as feelings of weakness, malaise, cold sweat, tremor, and disturbed consciousness occur, administration of this drug should be discontinued and appropriate measures should be taken.

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored for changes in their clinical symptoms including cough, dyspnoea, and pyrexia. If any abnormalities are observed, examinations including chest X-ray and chest CT scan should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms 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.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Oculomucocutaneous syndrome or erythema multiforme 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.

Use in the Elderly

Since elderly patients often have poor kidney function, this drug should be carefully administered through measures such as adjustment of dose or dosing interval in

reference to the creatinine clearance.
Also, in elderly patients, some cases of fall due to dizziness, somnolence, loss of consciousness, etc. leading to fracture have been reported, and therefore extra caution should be exercised.

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 (April 1, 2009 to June 7, 2012)

- Dizziness or disturbed consciousness-associated cases: 17 cases (no fatal cases)
- Hypoglycaemia: 3 cases (no fatal cases)
- Interstitial pneumonia-associated cases: 5 cases (no fatal cases)
- Shock or anaphylactoid symptoms-associated cases: 5 cases (no fatal cases)
- Oculomucocutaneous syndrome-associated cases: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 260,000 (July 1, 2011 to June 30, 2012)
Launched in Japan: June 2010

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Post herpetic neuralgia (hypertension)	150 mg (for 2 days)	**Dizziness** Day 1 of administration: The patient started receiving pregabalin at 150 mg/day for post herpetic neuralgia. Day 2 of administration (day of onset) (day of discontinuation): The patient fell due to dizziness, and then had laceration of face and laceration of tongue. Since haemorrhage due to laceration of tongue persisted, the patient was transported to another hospital. Administration of pregabalin was discontinued. 2 days after discontinuation: The patient was admitted to the hospital. 9 days after discontinuation: The patient recovered. 27 days after discontinuation: The patient was discharged from the hospital. 54 days after discontinuation: The patient and her family requested continued administration of pregabalin, and administration was resumed at 50 mg/day.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Pain (spinal column stenosis, osteoarthritis, nerve block)	300 mg (for 14 days) 450 mg (for 13 days)	**Hypoglycaemia** Day 1 of administration: The patient used gabapentin 1800 mg/day prescribed at the orthopedic clinic (off-label use). As long-term use of pregabalin became possible, gabapentin was switched to pregabalin 300 mg/day. Day 15 of administration: For further pain management, the dose of pregabalin was increased to 450 mg/day. Day 17 of administration:

				Loss of consciousness occurred at home. The family found the patient to be in this state several hours later. Blood glucose level was 21 mg/dL. Day 27 of administration (day of discontinuation): Blood glucose level was 31 mg/dL. Glucose was intravenously administered several times, but the symptoms did not improve. The patient was admitted to the hospital. Administration of pregabalin was discontinued. 1 day after discontinuation: The patient recovered. Estimated glomerular filtration rate (eGFR) level was 67.9.
	Concomitant medications: misoprostol, celecoxib, lansoprazole, etizolam			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 50s	Neuralgia (breast cancer, autoimmune thyroiditis, hypertension, diabetes mellitus, hyper-lipidaemia)	75 mg (for 21 days) 150 mg (for 67 days)	**Drug-induced lung disorder** 112 days before administration: The patient started receiving 4 cycles of fluorouracil, farmorubicin, and cyclophosphamide for breast cancer. 7 days before administration: Administration of paclitaxel once weekly started (12 cycles). Day 1 of administration: Oral administration of pregabalin 75 mg/day was started for peripheral neuropathy due to paclitaxel. Day 22 of administration: The dose of pregabalin was increased to 150 mg/day. Day 78 of administration: Administration of paclitaxel was completed. Day 82 of administration: Pyrexia in the 37°C range developed. Day 86 of administration: Since dyspnoea occurred with mild exercise, the patient visited the outpatient department. The chest CT scan showed ground-glass opacities, and drug-induced lung disorder was suspected. Day 88 of administration (day of discontinuation): Dyspnoea was aggravated, the patient was urgently admitted to the hospital. Administration of pregabalin was discontinued. 1 day after discontinuation: Bronchoscopy was performed, and the patient was diagnosed with drug-induced lung disorder. Steroid pulse therapy was performed from the same day for 3 days. Administration of ceftriaxone was also started because concurrent infection could not be ruled out. 4 days after discontinuation: The respiratory condition was improving and oral administration of prednisolone 40 mg (0.5 mg/kg) was started. 7 days after discontinuation: The chest CT showed improvement of the ground-glass opacities. 12 days after discontinuation: The dose of prednisolone was reduced to 30 mg. 19 days after discontinuation: The dose of prednisolone was reduced to 20 mg. 21 days after discontinuation:

				Dyspnoea disappeared and the patient was discharged from the hospital.
	Concomitant medications: paclitaxel, dexamethasone sodium phosphate, ranitidine hydrochloride, chlorpheniramine maleate, ciprofloxacin hydrochloride			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female 50s	Post herpetic neuralgia (immunodeficiency, congestive cardiac failure, protein-losing gastroenteropathy, intestinal lymphangiectasia, hypoalbuminaemia, hypocalcaemia, sepsis, staphylococcal sepsis, herpes zoster)	75 mg (for 1 day)	**Dyspnoea** 29 days before administration: The patient developed severe herpes zoster in the first division of the trigeminal nerve in the right face during long-term hospitalization due to severe immunodeficiency, severe hypoalbuminaemia, and severe congestive cardiac failure associated with severe protein-losing gastroenteropathy and severe intestinal lymphangiectasia. The patient complained of severe pain and was treated with antivirals, antidepressants, steroids, etc. For a time, the patient showed a trend toward a gradual improvement in the symptoms. 18 days before administration: The right subclavian central venous port had a bacterial infection, methicillin resistant Staphylococcus aureus (MRSA) sepsis occurred and the general condition of the patient became poor due to abdominal pain, vomiting, decreased blood pressure, etc. 11 days before administration: In week 3 after the onset of herpes zoster, severe pain like "a blow with a hammer" and facial hyperaesthesia occurred. The patient inadequately responded to the therapeutic drugs and the treatment provided by the pain clinic, and therefore administration of pregabalin was considered. Day 1 of administration: After dinner, the initial dose of pregabalin 75 mg was administered. On that day, the general condition was stable, but dyspnoea occurred 30 minutes after oral administration of pregabalin. Oxygen 5 L/min. was administered by mask, but respiratory failure did not improve. The chest X-ray showed acute aggravation of cardiac failure. Administration of bronchodilator and diuretics was not effective, and consequently the level of the patient's consciousness decreased. Blood pressure was in the 60 range, and oxygen saturation (SpO_2) was in the 80% level. The patient was transferred to the intensive care unit (ICU) 2 hours after oral administration of pregabalin, but the shock status did not improve. Dopamine hydrochloride and epinephrine were administered, and cardiac massage was performed, but the patient died about 2 hours after oral administration.

	Concomitant medications: furosemide, spironolactone, calcium L-aspartate, etizolam, enteral nutrition, alfacalcidol, heparin sodium, amitriptyline hydrochloride, prednisolone, aciclovir, pH4-treated acidic human normal immunoglobulin, codeine phosphate hydrate, sulbactam sodium/ampicillin sodium, human serum albumin, dopamine hydrochloride, metoclopramide hydrochloride, scopolamine butylbromide, vancomycin hydrochloride, omeprazole, sucralfate hydrate, fexofenadine hydrochloride, acetaminophen, extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Female 70s	Post herpetic neuralgia (neurogenic bladder, varicose vein, lumbar spinal stenosis)	75 mg (for 4 days)	**Drug eruption (erythema multiforme exudativum type)** 53 days before administration: The patient had post herpetic neuralgia and started receiving loxoprofen sodium hydrate at 180 mg/day. 32 days before administration: An epidural block was performed for post herpetic neuralgia, and administration of clonazepam 0.5 mg/day was started. 29 days before administration: Administration of clonazepam was discontinued. 28 days before administration: The symptoms did not improve and loxoprofen sodium hydrate was switched to carbamazepine 100 mg/day. 4 days before administration: Due to gastralgia and anorexia, administration of lansoprazole OD tablet 15 mg/day and rebamipide tablet 300 mg/day was started. Day 1 of administration: Administration of pregabalin 75 mg/day was started for post herpetic neuralgia. At that time, discontinuation of carbamazepine was instructed, but the patient continued oral administration of carbamazepine. Day 4 of administration (day of onset): Generalised erythema developed. Day 5 of administration (day of discontinuation): The patient visited reporting physician's department. Drug eruption was suspected and administration of pregabalin, lansoprazole OD, rebamipide, and carbamazepine was discontinued. Olopatadine hydrochloride, prednisolone valerate acetate, and clobetasol propionate were prescribed. 1 day after discontinuation: In addition to the spread of skin eruption, hyperaemia was observed in the lips and palpebral conjunctiva, the patient visited the emergency unit of this hospital and was immediately admitted to the hospital. Pain of the mouth was severe, administration of oral medications was difficult, and therefore drip infusion of prednisolone 50 mg/day was started. 2 days after discontinuation: A skin biopsy was performed from the abdomen. The result of drug lymphocyte stimulation test (DLST) was 341 cpm (measurement) and stimulation index (S.I.) of 358% for pregabalin, showing a positive result. Also for lansoprazole OD, the result was 257 cpm and S.I. of 194%, showing a positive result. 4 days after discontinuation: DLST was 349 cpm and S.I. of 104% for carbamazepine,

				showing a negative result. 6 days after discontinuation: The dose of prednisolone was reduced to 40 mg/day, and drip infusion was switched to oral administration. 8 days after discontinuation: Since skin eruption further improved, the dose of prednisolone was reduced to 30 mg/day. 9 days after discontinuation: Skin eruption mostly disappeared. 10 days after discontinuation: The dose of prednisolone was reduced to 20 mg/day. 14 days after discontinuation: The dose of prednisolone was reduced to 10 mg/day. 16 days after discontinuation: The dose of prednisolone was reduced to 5 mg/day. 18 days after discontinuation: Oral administration of prednisolone was completed. No recurrence was seen.
	Concomitant medications: lansoprazole, tolterodine tartrate, shakuyakukanzoto, mecobalamin, loxoprofen sodium hydrate, etizolam, hydroxyzine pamoate, carbamazepine, rebamipide			

2 **Methotrexate** (Tablet 2 mg, Capsule)

Brand Name (name of company)	RHEUMATREX CAPSULES 2 mg (Pfizer Japan Inc.) METHOTREXATE Tablets 2 mg "Tanabe" (Mitsubishi Tanabe Pharma Corporation) Metolate tablets 2 mg (Santen Pharmaceutical Co., Ltd.) TREXAMETTE Capsules 2 mg (Shiono Chemical Co., Ltd.) METHOTREXATE Capsules 2 mg "SAWAI" (Sawai Pharmaceutical Co., Ltd.) METHOTREXATE CAPSULES 2 mg "TOWA" (Towa Pharmaceutical Co., Ltd.) Methotrexate Cap. 2 mg "Mylan" (Mylan Seiyaku Ltd.)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	Rheumatoid arthritis, juvenile idiopathic arthritis associated with arthritic symptoms

PRECAUTIONS (underlined parts are revised)

Contraindications

Patients with active tuberculosis

Careful Administration

Patients infected with tuberculosis (especially patients with a history of tuberculosis and patients with findings of healing of tuberculosis on a chest X-ray)

Important Precautions

Prior to treatment, a sufficient interview regarding tuberculosis, chest X-ray, and tuberculin test should be performed. Chest CT, interferon-gamma response assay (QuantiFERON) also should be performed to check for tuberculosis infection, if necessary. If the patient has a history of tuberculosis or suspected tuberculosis, the patient should be referred to a physician who has clinical experience with tuberculosis. The following patients should be treated with an antitubercular agent prior to the treatment with this drug in principle.

(1) Patients whose chest image confirms or suggests old tuberculosis

(2) Patients who have been treated for tuberculosis (including extrapulmonary tuberculosis)

(3) Patients with strongly suspected infection based on a tuberculin test or

interferon-gamma response assay (QuantiFERON)

(4) Patients who have had close contact with patients with tuberculosis

Patients should be carefully monitored for tuberculous infection by performing periodic tests such as chest X-rays during administration of this drug as well. Additionally, patients should be instructed to contact their physician immediately if symptoms suggesting tuberculosis (e.g., persistent cough and pyrexia) are observed. Also, if active tuberculosis is confirmed, this drug should not be administered.

Adverse Reactions (clinically significant adverse reactions)

Tuberculosis: Tuberculosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration 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 (April 1, 2009 to May 16, 2012)

- Tuberculosis-associated cases: 7 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 308,000 (2011)

Launched in Japan: August 1999

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Rheumatoid arthritis (tuberculosis)	8 mg/week (unknown duration)	**Tuberculosis** Day 1 of administration: The patient started treatment with methotrexate at 8 mg/week, prednisolone at 5 mg, and infliximab (4 mg/kg/8 weeks) for rheumatoid arthritis. Day of discontinuation: Since cytopenia due to methotrexate occurred in association with decreased renal function, administration of methotrexate and infliximab was discontinued. 1 month after discontinuation (day of onset): While recovering from cytopenia, pyrexia occurred and then the patient was admitted to the hospital. The generalized imaging scan and culture test of various types of bacteria did not clearly show the focus of infection. Administration of meropenem 0.5 g × 3 was started, but the symptoms did not improve. Since disseminated intravascular coagulation gradually progressed, bone marrow aspiration was performed from the ilium, and then the patient was diagnosed with haemophagocytic syndrome (HPS). Bacterial infection, neoplastic disease, and autoimmune disease were not noted in the patient's background. Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) (1.7×10^3 copies/10^6cells) was detected in blood, thereby revealing reactivation of EBV. Also, the patient had a history of tuberculosis, received preventive oral administration of isoniazid for 9 months at the time of introduction to infliximab, but tuberculosis bacteria was cultured from bone marrow aspirate taken this time.
	Concomitant medications: infliximab (suspected concomitant drug), prednisolone (suspected concomitant drug)			

3 Influenza HA Vaccine

Brand Name (name of company)	Influenza HA Vaccine "KAKETSUKEN" (The Chemo-Sero-Therapeutic Research Institute) INFLUENZA HA VACCINE "BIKEN", FLUBIK HA, FLUBIK HA Syringe (The Research Foundation for Microbial Diseases of Osaka University) Influenza HA Vaccine "SEIKEN", Flu-Syringe "SEIKEN" (Denka Seiken Co., Ltd.) Influenza HA Vaccine "Kitasatodaiichisankyo" 0.5 mL, 1 mL, Influenza HA Vaccine "Kitasatodaiichisankyo" Syringe 0.5 mL (Kitasato Daiichi Sankyo Vaccine Co., Ltd.)
Therapeutic Category	Vaccines
Indications	Use for prevention of influenza

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Nephrotic syndrome: Nephrotic syndrome may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 3 years (April 1, 2009 to April 30, 2012)

- Nephrotic syndrome: 4 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
approximately 50.33 million for seasonal influenza vaccines (FY 2011)

Launched in Japan: September 1972

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Under age of 10	Vaccination (none)	0.5 mL once	**Nephrotic syndrome** The patient had no history of renal disorder. When the patient received influenza HA vaccine last year, he developed pyrexia and swelling on the extensor surface of the upper arm (vaccination site). Day of vaccination: The patient received influenza HA vaccine at Hospital A. 8 hours after vaccination: Since enlarged left axilla (measuring 6 cm) occurred and the vaccination site also swelled down to the elbow, the patient visited Hospital A again. The patient developed swollen lymph nodes in the left axilla and swelling on the extensor surface of the left upper arm (vaccination site). 1 day after vaccination: The patient had pyrexia in the 38°C range. The enlarged left axilla remitted to 2.5 cm. At Hospital A, an adverse reaction to influenza HA vaccine was suspected, ketotifen fumarate, cefdinir, betamethasone valerate/gentamicin sulfate ointment, and antibiotics-resistant lactic acid bacteriae preparation were prescribed. 3 days after vaccination: The patient visited Hospital A for generalized swelling again.

				Weight increased (16.0 → 16.5 kg). The patient had anasarca. Urine protein 21000 mg/dL (4+), uric blood (±), and no urinary sediment abnormalities were found. Urine specific gravity was not less than 1.030, serum albumin was 1.0 g/dL, total cholesterol was 315 mg/dL, blood urea nitrogen (BUN) was 13 mg/dL, and serum creatinine was 0.2 mg/dL. The patient was referred and admitted to Hospital B for nephrotic syndrome. Administration of ketotifen fumarate, cefdinir, betamethasone valerate/gentamicin sulfate ointment, and antibiotics-resistant lactic acid bacteriae preparation was completed. 5 days after vaccination: Oedema and proteinuria did not improve, intravenous administration of prednisolone sodium succinate for injection 2 mg/kg/day was started. 9 days after vaccination: Protein urine disappeared and oedema was improving. 12 days after vaccination: Oedema disappeared, and weight recovered to the pre-disease level. 17 days after vaccination: The patient was discharged from the hospital. Oral administration of prednisolone 2 mg/kg/day was continued on an outpatient basis. 21 days after vaccination: The patient recovered from nephrotic syndrome, swollen lymph nodes in the left axilla, swelling on the extensor surface of the left upper arm (vaccination site), and pyrexia.
	Concomitant medications: none			

Laboratory Examination

	3 days after vaccination	5 days after vaccination	9 days after vaccination
Urine protein (mg/dL)	21000	5260	-
Uric blood	(±)	2+	(-)
Urinary sediment, RBC	1-3	-	<1
Urinary sediment, WBC	7-10	-	<1
Urinary sediment, casts	(-)	-	-
WBC (/mm^3)	8500	13000	6710
Eosinophils (%)	15	0.6	0
Serum albumin (g/dL)	1.0	1.5	2.3
Serum Na (mEq/L)	133	136	133
Serum K (mEq/L)	4.3	5.4	4.2
Serum CI (mEq/L)	107	107	104
Total cholesterol (mg/dL)	315	-	516
Serum creatinine (mg/dL)	0.2	0.32	0.17
BUN (mg/dL)	13	20.3	11.5

3

Revision of Precautions (No. 238)

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 July 10, 2012 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 Antidiabetic agents

Metformin Hydrochloride

Brand Name	Glycoran Tablets 250 mg (Nippon Shinyaku Co., Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2 Miscellaneous metabolism agents-Miscellaneous

Eltrombopag Olamine

Brand Name	REVOLADE Tablets 12.5 mg, 25 mg (GlaxoSmithKline K.K.)
Precautions of Dosage and Administration	The effect of this drug is usually seen in 1 to 2 weeks. The same dose needs to be maintained for at least 2 weeks to confirm the effect. However, in patients with hepatic disorder, the time until the platelet count reaches a steady state is long, and therefore, the same dose needs to be maintained for at least 3 weeks to confirm the effect.

3 Miscellaneous metabolism agents-Miscellaneous

Denosumab (Genetical Recombination)

Brand Name	RANMARK SUBCUTANEOUS INJECTION 120 mg (Daiichi-Sankyo Company, Limited)
Important Precautions	Hypocalcaemia may occur. Patients should have their serum electrolyte levels, such as serum calcium and phosphorus, measured before the start of treatment. If hypocalcaemia is observed, pre-existing hypocalcaemia must be corrected prior to initiating therapy. Hypocalcaemia may occur at any time from within a few days after initiating the administration of the drug. Patients should be carefully monitored and serum electrolyte levels, such as serum calcium and phosphorus, should be measured on a regular basis. To reduce the risk of onset of hypocalcaemia, oral supplementation of calcium and vitamin D is required in all patients every day unless the corrected serum calcium levels are high.

Adverse Reactions (clinically significant adverse reactions)	**Hypocalcaemia**: Hypocalcaemia with symptoms including seizures, tetany, numbness, disorientation, and QT prolongation may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as intravenous administration of calcium should be taken. In addition, some cases of severe hypocalcaemia leading to fatal cases are reported overseas.

4 Antineoplastics-Miscellaneous

Temsirolimus

Brand Name	TORISEL Injection 25 mg (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Stomatitis**: Stomatitis, mouth ulceration, glossitis, oral pain, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. **Anaemia, decreased platelets, decreased leucocytes, decreased neutropils, and decreased lymphocytes**: Anaemia, decreased platelets, decreased leucocytes, decreased neutropils, and decreased lymphocyte may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

5 Antineoplastics-Miscellaneous

Nilotinib Hydrochloride Hydrate

Brand Name	Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Peripheral arterial occlusive disease:** Peripheral arterial occlusive diseases such as arteriosclerosis obliterans, peripheral ischaemia, and limb arterial thrombosis may occur, resulting in necrosis in some cases. Patients should be carefully monitored, and if intermittent claudication, pain, feeling cold, numbness, etc. are observed, appropriate measures such as discontinuing administration should be taken.

6 Acting mainly on mold

Voriconazole

Brand Name	VFEND 200 mg for Intravenous Use, VFEND Tablets 50 mg, 200 mg (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Hypoglycaemia**: Serious hypoglycaemia 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. **Disturbed consciousness**: Disturbed consciousness including loss of consciousness and depressed levels of consciousness 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.

7 Synthetic antibacterials

Sitafloxacin Hydrate

Brand Name	GRACEVIT TABLETS 50 mg, GRACEVIT FINE GRANULES 10% (Daiichi Sankyo Company, Limited)
Adverse Reactions (clinically significant	**Acute renal failure**: Acute renal failure may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should

adverse reactions)	be discontinued and appropriate measures should be taken. **Hypoglycaemia**: Hypoglycaemia may occur, resulting in hypoglycaemic coma in some cases. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. Hypoglycaemia more readily occurs in patients with diabetes mellitus, patients with renal impairment, and elderly patients.

8 Synthetic antibacterials

Ciprofloxacin, Ciprofloxacin Hydrochloride

Brand Name	Ciproxan Tablet 100, 200, Ciproxan-I.V. 200, 300 (Bayer Yakuhin, Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, and acute generalised exanthematous pustulosis 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.

9 Antivirals

Adefovir Pivoxil

Brand Name	Hepsera Tablets 10 (GlaxoSmithKline K.K.)
Important Precautions	Patients should be carefully monitored for renal impairment by measuring renal function levels such as serum creatinine during administration of this drug. Osteomalacia may occur from hypophosphatemia due to renal tubular disorder including Fanconi syndrome. Patients should be periodically monitored for changes in serum phosphorus and alkaline phosphatase, etc.
Adverse Reactions (clinically significant adverse reactions)	**Renal failure, severe renal impairment such as Fanconi syndrome**: Renal impairment, renal failure, renal tubular disorder, and Fanconi syndrome may occur. Patients should be carefully monitored through renal function tests, and if any abnormalities are observed, appropriate measures should be taken. In an overseas clinical study, decreased renal function was observed in pre-/post-liver transplant patients who were treated with this drug 10 mg/day. Many of these cases had risk factors for renal impairment including administration of ciclosporin or tacrolimus, decreased renal function, hypertension, diabetes mellitus, and transplant. In addition, administration of this drug was discontinued due to any kidney-related adverse events in 4% (19 of 467 patients) of these pre-/post transplant patients. Also, in other overseas clinical studies, increased serum creatinine or decreased serum phosphorus was reported in patients treated with this drug at a dose of 3 to 12 times the approved dose (10 mg/day) for 20 weeks or longer. **Osteomalacia**: Long-term administration of this drug may cause osteomalacia associated with bone pain, arthralgia, or muscular weakness from hypophosphatemia due to renal tubular disorder including Fanconi syndrome, resulting in fracture in some cases. When administering this drug over the long-term, patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

10 **Antivirals**

Famciclovir

Brand Name	Famvir Tab. 250 mg (Asahi Kasei Pharma Corporation)
Adverse Reactions (clinically significant adverse reactions)	**Acute renal failure**: Acute renal failure may occur. Patients should be carefully monitored through renal function tests, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin 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.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its 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 the drug 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 August 1, 2012)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Apomorphine Hydrochloride Hydrate Apokyn subcutaneous injection 30 mg	Kyowa Hakko Kirin Co., Ltd.	July 27, 2012
Rotavirus Vaccine, Live, Oral, Pentavalent RotaTeq Oral Solution	MSD K.K.	July 20, 2012
Gabapentin Enacarbil Regnite Tablets 300 mg	Astellas Pharma. Inc.	July 10, 2012
Bixalomer Kiklin Capsules 250 mg	Astellas Pharma. Inc.	June 26, 2012
Azithromycin Hydrate ZITHROMAC Intravenous use 500 mg ZITHROMAC 250 mg*1	Pfizer Japan Inc.	June 22, 2012
Aprepitant EMEND Capsules 125 mg, 80 mg, EMEND Capsules Set*2	Ono Pharmaceutical Co., Ltd.	June 22, 2012
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg*3	AstraZeneca K.K.	June 22, 2012
Pregabalin LYRICA Capsules 25 mg, 75 mg, 150 mg*4	Pfizer Japan Inc.	June 22, 2012
Lidocaine Penles Tape 18 mg*5	Nitto Denko Corporation	June 22, 2012
Dornase Alfa (Genetical Recombination) PULMOZYME Inhalation Solution 2.5 mg	Chugai Pharmaceutical Co., Ltd.	June 8, 2012
Rilpivirine Hydrochloride EDURANT Tablets 25 mg	Janssen Pharmaceutical K.K.	June 8, 2012
Miglustat BRAZAVES Capsule 100 mg	Actelion Pharmaceuticals Japan Ltd.	May 30, 2012
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg	Ferring Pharmaceutical Co., Ltd.	May 29, 2012
Mogamulizumab (Genetical Recombination) POTELIGEO Injection 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 29, 2012

Azilsartan AZILVA Tablets 20 mg, 40 mg	Takeda Pharmaceutical Company Limited	May 28, 2012
Oxycodone Hydrochloride Hydrate OXIFAST Injection 10 mg, 50 mg	Shionogi & Co., Ltd.	May 28, 2012
Thalidomide THALED CAPSULE 50, 100*[6]	Fujimoto Pharmaceutical Corporation	May 25, 2012
Doripenem Hydrate FINIBAX for Intravenous Infusion 0.25 g, 0.5 g, FINIBAX Kit for Intravenous Infusion 0.25 g*[7, 8]	Shionogi & Co., Ltd.	May 25, 2012
Thyrotropin Human Alfa (Genetical Recombination) THYROGEN for Intramuscular Injection 0.9 mg*[9]	Sato Pharmaceutical Co., Ltd.	May 25, 2012
Mometasone Furoate Hydrate NASONEX Nasal 50 μg 56 sprays, NASONEX Nasal 50 μg 112 sprays*[8]	MSD K.K.	May 25, 2012
Lidocaine/Propitocaine EMLA CREAM	Sato Pharmaceutical Co., Ltd.	May 14, 2012
Brimonidine Tartrate AIPHAGAN OPHTHALMIC SOLUTION 0.1%	Senju Pharmaceutical Co., Ltd.	May 11, 2012
Alendronate Sodium Hydrate Bonalon Bag for I.V. Infusion 900 μg	Teijin Pharma Limited	May 10, 2012
Caspofungin Acetate CANCIDAS for Intravenous Drip Infusion 50 mg, 70 mg	MSD K.K.	April 19, 2012
Eszopiclone Lunesta Tablets 1 mg, 2 mg, 3 mg	Eisai Co., Ltd.	April 18, 2012
Rivaroxaban Xarelto Tablets 10 mg, 15 mg	Bayer Yakuhin Ltd.	April 18, 2012
Atovaquone SAMTIREL Oral Suspension 15%	GlaxoSmithKline K.K.	April 17, 2012
Denosumab (Genetical Recombination) RANMARK SUBCUTANEOUS INJECTION 120 mg	Daiichi Sankyo Company, Limited	April 17, 2012
Crizotinib XALKORI Capsules 200 mg, 250 mg	Pfizer Japan Inc.	March 30, 2012
Duloxetine Hydrochloride Cymbalta Capsules 20 mg, 30 mg*[10]	Shionogi & Co., Ltd.	February 22, 2012

*1 An additional indication for “treatment of patients with pelvic inflammatory disease”

*2 An additional administration for “pediatrics (aged 12 and older)”

*3 An additional indication for “treatment of patients with suppression of recurrent gastric ulcer or duodenal ulcer associated with administration of low-doses aspirin”

*4 An additional indication for “treatment of pain in patients with fibromyalgia”

*5 An additional indication for “relief of pain at removal of molluscum contagiosum”

*6 An additional indication for “erythema nodosum leprosum”

*7 An additional indication for “pyogenic meningitis”

*8 An additional administration for “pediatrics”

*9 An additional indication for “adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of metastatic thyroid cancer”

*10 An additional indication for “treatment of pain in patients with diabetic neuropathy”