Pharmaceuticals and Medical Devices Safety Information

No. 306 October 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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Pharmaceuticals and Medical Devices Safety Information
No. 306 October 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

ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BUN	Blood urea nitrogen
CF	Colonfiberscopy
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
DIC	Disseminated intravascular coagulation
DLST	Drug lymphocyte stimulation test
DNA	Deoxyribonucleic acid
EPPV	Early Post-marketing Phase Vigilance
FGS	Fiberoptic gastroscopy
GBS	Guillain-Barre syndrome
HBc	Hepatitis B core
HBe	Hepatitis B envelope
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus-Deoxyribonucleic acid
HHV-6	Human herpesvirus 6
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgM-HBc	Immunoglobulin M-Hepatitis B core
IU	International unit
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
PLT	Platelet
T3	Triiodothyronine
T4	Thyroxine
T-Bill	Total bilirubin
TEN	Toxic epidermal necrolysis
TSH	Thyroid-stimulating hormone
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

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Adverse Reactions to Influenza Vaccine in the 2012 Season

1. Introduction

This section presents adverse reactions to influenza vaccine reported from October 2012 through the end of March 2013 (the 2012 season).

In the 2012 season, vaccination with trivalent influenza vaccine (including 2009 influenza [H1N1] and influenza A/H3N2 and B) was started in October. Based on the Operating Procedure for Influenza Vaccination (partially revised on September 29, 2011) and the Reporting Adverse Reactions to Influenza Vaccine (HSB Notification No. 0929-3 and PFSB Notification No. 0929-8, by the Secretary-General of Health Service Bureau and Pharmaceutical and Food Safety Bureau, MHLW, dated September 29, 2011; abolished on March 31, 2013), any adverse reactions considered to meet the Adverse Reaction Reporting Criteria were to be reported from the medical institution to the MHLW regardless of causality.

The data of adverse reactions reported by medical institutions were tabulated and evaluated by PMDA together with those reported by the marketing authorization holders (MAHs) as appropriate. In deaths and serious cases, the causalities were also evaluated based on evidence including opinions from experts. The necessity of safety measures was discussed.

These adverse reaction reports are investigated and reviewed on a regular basis at the Committee on Adverse Reactions of Immunization and Vaccine Department in the Health Sciences Council and Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the Joint Meeting) to determine the necessity of safety measures.[1)]

2. Reports of adverse reactions to influenza vaccines (2012 season)

Adverse reactions to influenza vaccines reported in the 2012 season are shown below. No significant safety concerns about the vaccination were identified at the Joint Meeting held in June 2013.

(1) Number of reported adverse reactions and reporting frequency

Table 1 shows the number of reported adverse reactions to the influenza vaccines and the reporting frequency calculated from the estimated number of vaccine persons based on the amount of vaccines distributed to the medical institutions.

Table 1 Number of reported adverse reactions and estimated number of vaccinated persons

	Adverse reactions reported by medical institutions			Number of adverse reactions reported by MAHs (serious adverse reaction report)*	
Estimated number of vaccinated persons (number of vaccinations)	Total number of reported adverse reactions (reporting frequency)	Number of reported serious cases (reporting frequency)		Number of reported serious cases (reporting frequency)	
			Number of reported deaths		Number of reported deaths
50,240,735 (as of March 31, 2013)	301 (0.0006%)	53 (0.0001%)	4 (0.000008%)	86 (0.00017%)	5 (0.000012%)

* The adverse reactions reported by MAHs were those cases determined to be serious in accordance with the Pharmaceutical Affairs Law Article 77-4-2 and may overlap with some other cases of adverse reaction reports by the medical institutions.

(2) Reported adverse reactions by sex and age group

The number of reported adverse reaction to influenza vaccine is shown by sex and age group in **Table 2** and **3**, respectively.

Table 2 Number of reports by sex

Sex	Number of adverse reactions reported by medical institutions	Number of adverse reactions reported by MAHs
Male	133	39
Female	167 (pregnant woman 0)	44 (pregnant woman 0)
Unknown	1	3
Total	301	86

Table 3 Number of reports by age

	Number of adverse reactions reported by medical institutions			Number of adverse reactions reported by MAHs	
Age	Number of reported adverse reactions	Number of reported serious cases		Number of reported serious cases	
			Number of reported deaths		Number of reported deaths
0	3	0	0	0	0
1-9 years	122	13	1	31	2
10-19 years	26	6	0	7	0
20-29 years	19	4	0	7	0
30-39 years	20	1	0	4	0
40-49 years	19	4	0	6	2
50-59 years	21	3	1	3	0
60-69 years	20	5	0	9	0
70-79 years	26	6	0	8	1
≥80 years	25	11	2	10	0
Unknown	0	0	0	1	0
Total	301	53	4	86	5

(3) Outline of reported adverse reactions

[1] Adverse reactions by System Organ Class

Adverse reactions to influenza vaccine reported for the 2012 season are presented by System Organ Class in the right column of **Table 4**. No marked difference was noted in comparison with the reports for the 2011 season.

Table 4 Comparison of adverse reaction reports between the 2011 season and the 2012 seasons

	2011 season		2012 season	
	Trivalent influenza vaccine		Trivalent influenza vaccine	
System Organ Class of adverse reaction*	Adverse reactions reported by medical institutions	Adverse reactions reported by MAHs	Adverse reactions reported by medical institutions	Adverse reactions reported by MAHs
Blood and lymphatic system disorders	5	3	4	4
Cardiac disorders	1	1	1	3
Ear and labyrinth disorders	0	1	0	0
Eye disorders	1	2	1	0
Gastrointestinal disorders	5	2	2	5
General disorders and administration site conditions	32	28	19	35
Hepatobiliary disorders	2	3	2	3
Immune system disorders	17	13	10	11
Infections and infestations	7	5	1	8
Investigations	2	6	1	4
Metabolism and nutrition disorders	2	1	0	2
Musculoskeletal and connective tissue disorders	2	11	1	6
Nervous system disorders	31	32	27	32
Renal and urinary disorders	0	2	3	4
Respiratory, thoracic and mediastinal disorders	15	11	1	4
Skin and subcutaneous tissue disorders	21	15	7	11
Endocrine disorders	1	0	0	0
Pregnancy, puerperium and perinatal conditions	0	1	0	0
Vascular disorders	1	1	1	3
Injury, poisoning and procedural complications	1	0	1	0
Reproductive system and breast disorders	0	0	1	0
Total	146	138	83	135

* Adverse reaction terms were coded in accordance with the MedDRA/J Ver. 16.0.

* With regard to adverse reactions reported by medical institutions, adverse reactions that were considered serious by the reporting physicians were tabulated.

[2] Fatal case reporting

Nine cases of post-vaccination death were reported up to May 14, 2013. Experts assessed that 8 cases were likely caused by exacerbation or recurrence of an underlying diseases, and that none of these deaths had a direct, clear causality to the vaccination. The following opinions on idiopathic

thrombocytopenic purpura reported in one fatal case were raised from the experts; the death may be associated with the vaccination or most likely caused by an adverse reaction to the drug used for the treatment of an underlying disorder. Thrombocytopenic purpura is one of the expected adverse reactions listed in the package insert of influenza vaccine and subject to reporting within 28 days of onset according to the Adverse Reaction Reporting Criteria.[Note 1)]

[3] Guillain-Barre syndrome, acute disseminated encephalomyelitis

A total of 36 cases of adverse reactions were identified as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis. As shown in **Table 5**, based on the evidence including the expert assessment, the possibility of Guillain-Barre syndrome for 5 cases and acute disseminated encephalomyelitis for 6 cases could not be ruled out.

Table 5 Adverse reaction reports for which the possibility of Guillain-Barre syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) could not be ruled out according to the expert assessment

Expert assessment	Reported by	Age	Sex	Underlying diseases	Days after vaccination
Cases for which possible GBS could not be ruled out	Medical institution	40s	Male	Nephrotic syndrome, hyperlipidemia, hyperuricemia, osteonecrosis	10 days
	MAHs	60s	Female	Hypertension, dyslipidemia, impaired glucose tolerance	4 days
		50s	Male	Hypertension, diabetes mellitus	21 days
		20s	Female	Thyroid neoplasm	1 days
		60s	Female	Breast cancer	13 days
Cases for which possible ADEM could not be ruled out	Medical institution	Under age of 10	Male	None	17 days
		10s	Male	Aplastic anemia, myocarditis	12 days
		50s	Female	None	19 days
		60s	Male	None	18 days
	MAHs	Under age of 10	Male	Limb injury, pneumonia	28 days
		60s	Female	None	26 days

Initial symptoms of Guillain-Barre syndrome include muscular weakness in legs, gait disorder, muscular weakness in both hands and arms, muscular weakness in bilateral facial muscle, double vision and difficult swallowing food. Muscle weakness advances rapidly, within 1 day to 2 weeks of onset, regardless of where it starts. Drug-induced Guillain-Barre syndrome often occurs within 2 weeks of treatment; however, symptoms may occur after several months. Occurrence of influenza vaccine-induced Guillain-Barre syndrome peaks at 2 weeks after vaccination. Symptoms mostly occur within 6 weeks.[3)]

Acute disseminated encephalomyelitis generally occurs within 1 to 4 weeks after vaccination. The symptoms of acute disseminated encephalomyelitis appear rapidly, beginning with headache, pyrexia, and vomiting, and occur frequently with the disturbed consciousness. The severity of disturbed consciousness varies from mild somnolence to deep coma. Convulsion often occurs and meningeal irritation signs such as stiff neck may also occur. Time to onset is within one month in most cases. Acute disseminated encephalomyelitis with central nervous and optic neuritis complications occurs at a frequency of 1 to 3.5 persons per 10 million vaccinations. Frequency of acute disseminated encephalomyelitis may increase if mild cases without sequelae are included. An estimated frequency of transient acute demyelinating lesions is less than one in 100 000 vaccinations.[4)]

Guillain-Barre syndrome and acute disseminated encephalomyelitis are listed as adverse reactions

to influenza vaccine in the package insert and subject to reporting within 28 days according to the Adverse Reaction Reporting Criteria.

[4] Anaphylaxis

A total of 25 cases of adverse reactions were reported as possible anaphylaxis,[Note 2)] of these, 7 cases (including 7 serious cases) were assessed as anaphylaxis of Level 3 or higher of Brighton Criteria. Cases of Level 3 or higher of the Brighton Criteria were reported at a frequency of 1 out of 1 million vaccinations.

There were no specific lots in which anaphylaxis was reported more than in other lots.

Note 1) Reporting Adverse Reaction for Routine Vaccination (provisional English translation); HSB Notification No. 0330-3 and PFSB Notification No. 0330-1, by the Secretary-General of HSB and PFSB, MHLW, dated March 30, 2013

Note 2) Includes cases reported as anaphylaxis, anaphylactic reaction, anaphylactic shock and anaphylactoid reaction.

3. Safety measures hereafter

As provided in Reporting Adverse Reaction for Routine Vaccination (HSB Notification No. 0330-3 and PFSB Notification No. 0330-1, by the Secretary-General of HSB and PFSB, MHLW, dated March 30, 2013),[2)] medical institutions are requested to promptly report any adverse reactions considered to meet the Adverse Reaction Reporting Criteria even if the causality is unclear.

In addition, medical institutions are requested to continue to exercise caution for the following points concerning anaphylaxis in the 2013 season:

(1) Vaccine recipients should be closely monitored for about 30 minutes after vaccination.
(2) If any symptoms suggesting anaphylaxis is observed, appropriate measures should be taken.
(3) Vaccine recipients and their guardians should be advised to consult a physician immediately if any abnormalities are observed after vaccination.

MHLW/PMDA will continue to collect safety information of influenza vaccine including adverse reaction reports and to conduct safety measures.

<References>

1) Ministry of Health, Labour and Welfare: Distributed Materials 1-3 for the 2013 Committee on Adverse Reactions of Immunization and Vaccine Department in the Health Sciences Council (the second meeting) and 2013 Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the second meeting) (the Joint Meeting), Report of Adverse Reactions to Influenza Vaccines
http://www.mhlw.go.jp/stf/shingi/2r98520000034lcq-att/2r98520000034lsl.pdf (only available in Japanese language)
2) Reporting Adverse Reaction for Routine Vaccination; HSB Notification No. 0330-3 and PFSB Notification No. 0330-1, by the Secretary-General of HSB and PFSB, MHLW, dated March 30, 2013
http://www.mhlw.go.jp/topics/bcg/tp250330-1.html (only available in Japanese language)
3) Manuals for Management of Individual Serious Adverse Drug Reactions, Guillain-Barre syndrome
http://www.info.pmda.go.jp/juutoku/file/jfm0905002.pdf (only available in Japanese language)
4) Manuals for Management of Individual Serious Adverse Drug Reactions, Acute disseminated encephalomyelitis
http://www.info.pmda.go.jp/juutoku/file/jfm1104009.pdf (only available in Japanese language)

Reference: Adverse Reaction Reporting Criteria

<Routine vaccination>

Symptoms	Time to onset
Anaphylaxis	4 hours
Hepatic dysfunction	28 days
Interstitial pneumonia	28 days
Acute disseminated encephalomyelitis	28 days
Guillain-Barre syndrome	28 days
Convulsion	7 days
Vasculitis	28 days
Thrombocytopenic purpura	28 days
Asthmatic attack	24 hours
Nephrotic syndrome	28 days
Encephalitis or encephalopathy	28 days
Oculomucocutaneous syndrome	28 days
Other symptoms considered to be strongly associated with the vaccination by the physician, requiring hospital admission, resulting in death or physical dysfunction, or possibly resulting in death or physical dysfunction	Time frame in which the event was considered to be strongly associated with the vaccination by the physician

Except for Other reactions, any event occurring within the specific time frame is subject to mandatory reporting to the government regardless of causality according to the Preventive Vaccination Law and associated related rules.

<Voluntary vaccination>

Adverse reactions or infections associated with voluntary vaccinations should be reported when reporting is necessary to prevent the occurrence or spread of a health hazards. See below for specific cases subject to reporting. Adverse reactions and infections of unclear association with vaccinations may also be subject to reporting.

(1) Death
(2) Disability
(3) Events that may result in death
(4) Events that may result in disability
(5) Requiring hospital admission or prolonged hospitalization for treatment [except for events in (3) and (4)]
(6) Severe events corresponding to those in (1) to (5)
(7) Congenital disease or anomaly in the next generation
(8) Onset of infections suspected of being caused by use of the drug
(9) Onset of unknown events which are non-mild and unexpected from the package insert, other than (1) to (8)

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated September 17, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Propylthiouracil

Brand Name (name of company)	1) THIURAGYL tablets 50 mg (Mitsubishi Tanabe Pharma Corporation) 2) PROPACIL Tablet 50 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Thyroid and parathyroid hormone preparations
Indications	Hyperthyroidism

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Drug-induced hypersensitivity syndrome: Rash and pyrexia may occur as the initial symptoms followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, swollen lymph nodes, leukocytosis, eosinophilia, and atypical lymphocytes. Patients should be carefully monitored, and if such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken. The reactivation of viruses including Human Herpes virus 6 (HHV-6) has been found to be frequently associated with drug-induced hypersensitivity syndrome. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus 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 and 3 months (April 2010 to July 2013)

- Drug-induced hypersensitivity syndrome-associated cases: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 50,000 (2012)

Launched in Japan: (1) May 1968
(2) February 1966

<Reference> Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions, Drug-Induced Hypersensitivity Syndrome

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Basedow's disease (diabetes mellitus, iron deficiency anaemia,	150 mg/ day for 38 days	**Drug-induced hypersensitivity syndrome** Day 1 of administration: The patient started receiving propylthiouracil 150 mg/day at Hospital A. Thyroid-stimulating hormone (TSH) ≤ 0.005, Triiodothyronine (T3) 1.84, and Thyroxine (T4) 16.0. Day 33 of administration:

		hypertension)		Due to urticaria, betamethasone/d-chlorpheniramine maleate (3 tablets daily for 3 days) was prescribed at Hospital A. Malaise also occurred. Day 38 of administration (day of discontinuation): The patient visited Hospital B and then was referred to this hospital due to a liver disorder, generalised rash, and renal disorder. 1 day after discontinuation: The patient visited this hospital and was urgently admitted. Liver disorder, cholecystitis, and skin eruption were observed. Body temperature 37.7°C (at visit), 38.0°C (evening), and 38.7°C (night). 2 days after discontinuation: Pyrexia was found, administration of antibiotics was started. Erythema and oedema were also found. Body temperature 38.5°C (early morning), 38.1°C (morning), and 39.4°C (evening). 3 days after discontinuation: Drug lymphocyte stimulation test (DLST) was positive for propylthiouracil. 5 days after discontinuation: HHV6 immunoglobulin G (IgG) < 10 (normal range is <10) 6 days after discontinuation: The patient was considered to have drug-induced allergy. After the start of steroid pulse therapy, the symptoms improved. 10 days after discontinuation: Potassium iodide was prescribed for the thyroid gland, and administration of nafamostat mesilate was started for a disseminated intravascular coagulation (DIC) (score, 6 points). 11 days after discontinuation: HHV6 deoxyribonucleic acid (DNA) quantitative 6.0×10^4 copies (the number of copies per 1,000,000) 18 days after discontinuation: Swollen lymph nodes were noted HHV6 immunoglobulin M (IgM) < 10 (normal range is < 10), HHV IgG 80 (normal range is < 10) 39 days after discontinuation: During treatment with prednisolone after steroid pulse, the patient was discharged from hospital despite having diarrhoea. 41 days after discontinuation: The patient visited the outpatient department due to diarrhoea, vomiting, and hypoglycaemia, and was urgently admitted to the hospital for blood pressure 70 mmHg. As adrenal insufficiency developed, administration of catecholamine and steroid therapy was continued. 45 days after discontinuation: Administration of ganciclovir was started for DIC and blood cytomegalovirus (CMV) positive. Platelet transfusion was performed for cytopenia. Because diarrhoea was noted, administration of loperamide hydrochloride was started. 72 days after discontinuation: Oesophageal candidiasis was noted with chest pain, application of miconazole gel was started. 73 days after discontinuation:

				Lower colonfiberscopy (CF) (large bowel endoscopy) showed a finding of CMV enterocolitis. 74 days after discontinuation: Fiberoptic gastroscopy (FGS) (upper gastrointestinal tract endoscopy) showed the oesophageal lesion and improvement of duodenum. 76 days after discontinuation: The patient had pneumonia. The worsened respiratory status suggesting aspiration pneumonia was noted, she died in the afternoon (cause of death was pneumonia).
	Concomitant medications: betamethasone/d-chlorpheniramine maleate, glimepiride, valsartan, allopurinol, furosemide, sodium picosulfate hydrate			

Laboratory Examination

Test date / Parameter	1 day after discontinuation	12 days after discontinuation	24 days after discontinuation	40 days after discontinuation	74 days after discontinuation
WBC (/mm^3)	10,700	7,700	7,200	5,400	11,200
Neutrophils (%)	69.5	64	58.4	27.2	-
Eosinophils (%)	6.0	-	0.5	0.1	-
Basophils (%)	0.8	-	0.7	0.1	-
Monocytes (%)	8.1	-	8.6	8.8	-
Lymphocytes (%)	21.6	25	31.8	13.8	-
PLT (10^4/mm^3)	23.7	10.3	15.5	21.2	1.4
AST (GOT) (IU/L)	342	24	11	51	26
ALT (GPT) (IU/L)	531	97	25	79	34
LDH (IU/L)	698	290	220	202	256
γ-GTP (IU/L)	283	242	164	111	-
Total bilirubin (mg/dL)	3.5	2.2	-	0.5	-
BUN (mg/dL)	48	34	33	68	32
Serum creatinine (mg/dL)	1.75	1.26	1.13	4.62	2.62
CRP (mg/dL)	3.9	0.6	-	10.0	5.3

2 Bortezomib

Brand Name (name of company)	VELCADE Injection 3 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Multiple myeloma

PRECAUTIONS (underlined parts are revised)

Important Precautions

<u>Hepatitis due to reactivation of hepatitis B virus may occur in hepatitis B virus carriers or HBs antigen-negative patients with HBc antibody-positive or HBs antibody-positive after administration of this drug. Prior to treatment, patient should be checked for hepatitis virus infection and appropriate measures should be taken before administration of this drug. After the start of administration of this drug, attention to the occurrence of signs or symptoms related to reactivation of hepatitis B virus should be paid by continuously monitoring results of liver function tests or hepatitis virus markers.</u>

Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction**: Hepatic dysfunction (including those due to reactivation of hepatitis B virus) with increased AST (GOT), increased ALT (GPT), increased γ-GTP, increased Al-P, and increased blood bilirubin, etc. may occur. Patient should be carefully monitored, if any abnormalities are observed, appropriate measures such as discontinuation of 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 and 3 months (April 2010 to July 2013) • Cases associated with reactivation of hepatitis B virus: 4 cases (no fatal cases) The number of patients using this drug per year estimated by MAHs: Approximately 6,000 (January 2012 to December 2012) Launched in Japan: December 2006

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Multiple myeloma (hypertension, hepatitis virus carrier, peripheral neuropathy)	1.1 mg for 67 days	**Hepatitis B, liver disorder** Approximately 7 years before administration: Hepatitis B surface (HBs) antigen was negative. Approximately 3 years before administration: The patient received initial blood transfusion. Approximately 1 year and 2 months before administration: HBs antigen and hepatitis B envelope (HBe) antigen were negative. Hepatitis B core (HBc) antibody was positive Blood transfusion (4th) was performed. At this point, the patient was already infected with hepatitis B virus (HBV). 81 days before administration: HBs antigen and HBe antigen were negative HBc antibody was positive 3 days before administration: Liver disorder was not found. Packed red blood cells (2 units) were transfused. 1 day before administration: The patient was admitted to hospital for administration of bortezomib. Day 1 of administration: The first cycle of administration of bortezomib was started. 11 days after administration: The first cycle of administration of bortezomib was discontinued. 12 days after administration: The patient was discharged from the hospital. 17 days after administration (day of onset): Pyrexia and urinary incontinence developed, the patient was transported by ambulance. The patient experienced liver disorder with AST 959 IU/L, ALT 685 IU/L, γGTP 590 IU/L, and total bilirubin 2.27 mg/dL and was admitted to the hospital. 1 day after onset: Medical treatment was performed with monoammonium glycyrrhizinate/glycine/L-cysteine injection (for 3 days) for liver disorder. 2 days after onset:

				The patient was positive for HBs antigen, HBe antigen, and HBV-DNA, the patient condition was diagnosed as de novo hepatitis B. 14 days after onset: AST decreased to 22 IU/L, ALT to 19 IU/L, γGTP to 156 IU/L, and total bilirubin to 0.86 mg/dL, liver disorder improved, but anaemia progressed. 15 days after onset: Packed red blood cells (2 units) were transfused. Concomitant pneumonia occurred, administration of cefepime dihydrochloride hydrate was started (for 8 days). 22 days after onset: AST 25 IU/L, ALT 17 IU/L, γGTP 86 IU/L, and total bilirubin 0.42 mg/dL. 26 days after onset: The patient was discharge from the hospital. 39 days after onset: Oral administration of entecavir hydrate (0.5 mg/day) was started for hepatitis B. 42 days after onset: AST 26 IU/L, ALT 20 IU/L, γGTP 70 IU/L, total bilirubin 0.53 mg/dL. 46 days after onset: The second cycle of administration of bortezomib was started. The patient was positive for HBe antigen and HBV-DNA, and did not recover from hepatitis B at this point. 50 days after onset (day of discontinuation): In the second cycle, the second administration of bortezomib was performed. 3 days after discontinuation: As anaemia progressed, packed red blood cells (2 units) were transfused. 6 days after discontinuation: Back pain and pyrexia was noted, the patient visited the hospital urgently. The patient was admitted to the hospital for pain control. 7 days after discontinuation: Back pain increased. Respiratory condition and consciousness level worsened. Cardiopulmonary resuscitation was performed and a mechanical ventilator was set up, but no improvement was observed. Due to disease progression, the patient died. [Autopsy findings] Compression fracture of the sixth thoracic vertebra, submucosal haemorrhage from the ileocecal region to descending colon, bronchopneumonia, and cardiac hypertrophy.
	Concomitant medications: dexamethasone sodium phosphate, amlodipine besilate, alendronate sodium hydrate, famotidine, betamethasone/d-chlorpheniramine maleate, packed red blood cells, cefepime dihydrochloride hydrate			

Laboratory Examination

	81 days before administra-tion	1 day before administra-tion	5 days after administra-tion	17 days after administration (day of onset)	2 days after onset	14 days after onset	22 days after onset	42 days after onset	46 days after onset

AST (IU/L)	-	14	15	959	147	22	25	26	-
ALT (IU/L)	-	13	17	685	-	19	17	20	-
LDH (IU/L)	-	200	160	1,319	227	252	196	257	-
ALP (IU/L)	-	192	174	1,600	1,218	465	274	249	-
γ-GTP (IU/L)	-	30	32	590	419	156	86	70	-
Total bilirubin (mg/dL)	-	0.43	0.25	2.27	3.47	0.86	0.42	0.53	-
HBs antigen	Negative	-	-	-	Positive	-	-	-	-
HBc antibody	Positive	-	-	-	Positive	-	-	-	-
HBe antigen	Negative	-	-	-	Positive	-	-	-	Positive
IgM-HBc antibody	-	-	-	-	Negative	-	-	-	-
HBV-DNA quantitative	-	-	-	-	5.8	-	-	-	6.9
HBV-DNA	-	-	-	-	Positive	-	-	-	Positive

3 Minocycline Hydrochloride (oral dosage form, injectable dosage form)

Brand Name (name of company)	(1) MINOMYCIN GRANULES 2% (Pfizer Japan Inc.) and the others (2) MINOMYCIN TABLETS 50 mg, 100 mg, MINOMYCIN CAPSULES 50 mg, 100 mg (Pfizer Japan Inc.) and the others (3) MINOMYCIN INTRAVENOUS 100 mg (FOR DRIP USE) (Pfizer Japan Inc.) and the others
Therapeutic Category	Acting mainly on gram-positive bacteria, gram-negative bacteria, rickettsia and chlamydia
Indications	(1) <Applicable microorganisms> Minocycline-susceptible strains of Staphylococcus, Streptococcus, Pneumococcus, Enterococcus, Bacillus anthracis, Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Rickettsia (Orientia tsutsugamushi), Chlamydia, and Mycoplasma pneumoniae <Applicable conditions> Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, osteomyelitis, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, dacryocystitis, hordeolum, otitis media, sinusitis, suppurative sialoadenitis, periodontal inflammation, infectious stomatitis, scarlet fever, anthrax, tsutsugamushi disease, psittacosis (2) <Applicable microorganisms> Minocycline-susceptible strains of Staphylococcus, Streptococcus, Pneumococcus, Enterococcus, Neisseria gonorrhoeae, Bacillus anthracis, Escherichia coli, Shigella dysenteriae, Citrobacter, Klebsiella, Enterobacter, Proteus, Morganella morganii, Providencia, Pseudomonas aeruginosa, Treponema pallidum, Rickettsia (Orientia tsutsugamushi), Chlamydia, and Mycoplasma pneumoniae <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, osteomyelitis, pharyngitis/laryngitis, tonsillitis (including peritonsillitis), acute bronchitis, pneumonia, lung abscess, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, prostatitis (acute/chronic), epididymitis, urethritis, Neisseria gonorrhoeae infection, syphilis, peritonitis, infectious enteritis,

	vulvitis, bacterial vaginitis, intrauterine infection, dacryocystitis, hordeolum, otitis externa, otitis media, sinusitis, suppurative sialoadenitis, periodontal inflammation, pericoronitis, maxillary sinusitis, jaw inflammation, anthrax, tsutsugamushi disease, psittacosis (3) <Applicable microorganisms> Minocycline-susceptible strains of Staphylococcus aureus, Streptococcus, Pneumococcus, Enterococcus, Moraxella lacunata (Morax-Axenfeld bacillus), Bacillus anthracis, Escherichia coli, Klebsiella, Enterobacter, Hemophilus influenzae, Pseudomonas fluorescens, Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas (Xanthomonas) maltophilia, Acinetobacter, Flavobacterium, Legionella pneumophila, Rickettsia (Orientia tsutsugamushi), Chlamydia, and Mycoplasma pneumoniae <Applicable conditions> Sepsis, deep-seated skin infections, chronic pyoderma, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, peritonitis, anthrax, scrub typhus, psittacosis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Polyarteritis nodosa, microscopic polyangiitis: Polyarteritis nodosa or microscopic polyangiitis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, malaise, decreased weight, arthralgia, livedo reticularis, and numbness are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Autoimmune hepatitis: Autoimmune hepatitis with antinuclear antibody positive may occur in patients having received this drug for a long period. Patients should be carefully monitored through periodic tests, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, exfoliative dermatitis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme or exfoliative dermatitis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, erythema, pruritus, ocular hyperaemia, and stomatitis 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 3 months (April 2010 to July 2013)

- Vasculitis-associated cases: 2 cases (no fatal cases)
- Autoimmune hepatitis: 1 case (no fatal cases)
- Erythema multiforme: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 1.74 million (March 2012 to February 2013)

Launched in Japan: September 1981 (capsules 50 mg)
November 1981 (tablets 100 mg)
July 1984 (tablets 50 mg)
September 2001 (capsules 100 mg)
June 2008 (granules, for intravenous drip infusion)

(Note) The drugs are designated as those requiring the preparation of Drug guides for patients.

Case Summaries

No.	Patient		Daily dose/	Adverse reactions
	Sex/	Reason for		Clinical course and therapeutic measures

	Age	use (complications)	Treatment duration	
1	Male 40s	Acne (none)	Unknown Unknown	**Autoimmune hepatitis** Day 1 of administration: The patient started receiving minocycline hydrochloride for acne vulgaris on the face. Day of onset: Because malaise occurred, the patient visited hospital. AST (GOT) 779 IU/L, ALT (GPT) 1384 IU/L, and total bilirubin (T-Bil) 5.5 mg/dL, liver disorder was noted. Date unknown: Drug-induced liver disorder was suspected, administration of minocycline hydrochloride was discontinued, but T-Bil increased to 8.9 mg/dL. Liver biopsy was performed. Autoimmune hepatitis (AIH) score in the international scoring system was 13 (probable diagnosis) before treatment. A problem was how to differentiate it from drug-induced liver disorder associated with immune abnormality. Based on the pathological findings and clinical course, autoimmune hepatitis was suspected, and administration of prednisolone 60 mg/day was started as a medical procedure. Date unknown: Liver function improved, the patient was discharged from hospital. DLST test result was positive.
	Concomitant medications: none			

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Antibiotic therapy (eczema)	200 mg/ day for 10 days	**Erythematous rash** 22 days before administration: The patient's left forearm was scratched by a stray cat. 4 days before administration: Due to worsening of the wound, the patient visited a dermatology clinic, and then administration of levofloxacin hydrate was started. 2 days before administration: Oral administration of levofloxacin hydrate was discontinued, and administration of cefcapene pivoxil hydrochloride hydrate was started. Day 1 of administration: Administration of cefcapene pivoxil hydrochloride hydrate was discontinued, and administration of minocycline hydrochloride 200 mg/day was started. Around Day 2 of administration: Drug eruption (erythema exudativum multiforme) was observed throughout the body. Day 5 of administration: Administration of cetirizine hydrochloride and emedastine fumarate was discontinued. Day 6 of administration: Slight fever also developed, the patient was referred to and visited the dermatology department of a general hospital. Pustules, erosion, and redness in the left forearm, and swollen

				lymph nodes in the left axillary also developed. Small papules, pustules, and erythema were observed on the limbs and trunk. Day 8 of administration (day of onset): Forearm erosion disappeared, but erythema spread systemically, coalescence was found. Administration of prednisolone 15 mg/day was started. Day 10 of administration: Skin eruption further spread and formation of blisters was noted, administration of minocycline hydrochloride was discontinued. The patient was admitted to the dermatology department of a general hospital. The dose of prednisolone was increased to 30 mg/day. 4 days after discontinuation: Because the color of the skin eruption showed a tendency toward fading, the patient was discharged from the hospital. 7 days after discontinuation: The dose of prednisolone was reduced to 20 mg/day. 25 days after discontinuation: The patient recovered from drug eruption (erythema exudativum multiforme). Administration of prednisolone was discontinued with dose reduction.
	Concomitant medications: cetirizine hydrochloride, ascorbic acid/calcium pantothenate, levofloxacin hydrate, cefcapene pivoxil hydrochloride hydrate, emedastine fumarate			

4 Losartan Potassium

Brand Name (name of company)	NU-LOTAN Tablets 25 mg, 50 mg, 100 mg (MSD K.K) and the others
Therapeutic Category	Antihypertensives
Indications	・ Hypertension ・ Diabetic nephropathy in the patients with type 2 diabetes mellitus with hypertension and proteinuria

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Hyponatraemia: Hyponatraemia with malaise, inappetence, queasy, vomiting, convulsion, disturbed consciousness, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken immediately.

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 3 months (April 2010 to July 2013)

- Hyponatraemia: 2 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs:
Approximately 797,000 (January 2012 to December 2012)

Launched in Japan: August 1998 (tablets 25 mg, 50 mg)
March 2009 (tablets 100 mg)

(Note) The drugs are designated as those requiring the preparation of Drug guides for patients.

Case Summary

No.	Patient		Daily dose/	Adverse reactions
	Sex/	Reason for		Clinical course and therapeutic measures

	Age	use (complications)	Treatment duration	
1	Female 70s	Hypertension (hepatic cirrhosis)	50 mg for 21 days	**Hyponatraemia** Day 1 of administration: The patient was admitted to hospital (The reason for admission is unknown). Due to admission, the prescription was changed from candesartan cilexetil to losartan potassium. Administration of other concomitant medications was continued. Day 5 of administration (day of onset): Depressed level of consciousness was observed. Blood tests performed for detailed examination of the cause and hyponatremia was noted. Sodium (Na) was 120 mEq/L. Day 19 of administration: After oral sodium chloride was prescribed, the symptoms temporarily improved. On the same day, Na level was 127 mEq/L, showing a decrease again. Day 21 of administration: Administration of losartan potassium was discontinued. 2 days after discontinuation: Na level was 135 mEq/L, showing improvement, and the patient's level of consciousness also improved. The patient recovered from hyponatremia.
	Concomitant medications: rebamipide, ursodeoxycholic acid, benfotiamine/B6/B12, propranolol hydrochloride			

Laboratory Examination

	Day 5 of administration (day of onset)	Day 19 of administration	2 days after discontinuation
Na (mEq/L)	120	127	135

Note: This case is an adverse reaction reported before April 2010 and for which a causal relationship cannot be ruled out.

3

Revision of Precautions (No. 250)

(1) Drugs

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 September 17, 2013 (excluding those presented in "2. Important Safety Information" of the preceding Bulletin and this Bulletins).

1 Antipyretics and analgesics, anti-inflammatory agents

Celecoxib

Brand Name	Celecox Tablets 100 mg, 200 mg (Astellas Pharma Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Interstitial pneumonia**: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, or abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken. **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis, exfoliative dermatitis**: Serious and possibly fatal skin symptoms such as toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, acute generalised exanthematous pustulosis, and exfoliative dermatitis have been reported. Patients should be carefully monitored, and if rash, mucous membrane disorder or any signs related to hypersensitivity are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

2 Psychotropics

Sertraline Hydrochloride

Brand Name	J ZOLOFT Tablets 25 mg, 50 mg (Pfizer Japan Inc.)
Careful Administration	Patients with or medical history of prolonged QT, patients treated with drugs that are known to cause prolonged QT, patients with marked bradycardia, or hypokalaemia, etc.
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including Torsades de pointes)**: Prolonged QT or ventricular tachycardia (including torsades de pointes) 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.

3

Anticoagulants

Fondaparinux Sodium

Brand Name	Arixtra Injection 1.5 mg, 2.5 mg, 5 mg, 7.5 mg (GlaxoSmithKline K.K.)
Important Precautions	The injection needle cover for this drug contains natural rubber latex, which may cause allergic reaction. A medical interview should be performed prior to administration of this drug. In addition, patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Shock, anaphylaxis**: Shock or anaphylaxis (including decreased blood pressure, tachycardia, and urticaria) 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

Miscellaneous metabolism agents-Miscellaneous

Zoledronic Acid Hydrate

Brand Name	ZOMETA for i.v. infusion 4 mg/5 mL, 4 mg/100 mL (Novartis Pharma K.K.)
Important Precautions	If hypocalcaemia with any clinical symptoms and signs (prolonged QT, convulsion, tetany, numbness, disorientation, etc.) is observed, intravenous administration of calcium is effective.
Adverse Reactions (clinically significant adverse reactions)	**Hypocalcaemia**: Hypocalcaemia with prolonged QT, convulsion, tetany, numbness, disorientation, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as intravenous administration of calcium should be taken.

5

Antineoplastics-Miscellaneous

Erlotinib Hydrochloride

Brand Name	TARCEVA Tablets 25 mg, 100 mg, 150 mg (Chugai Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Severe skin disorders**: Severe skin disorders (including rash such as acneiform rash, nail disorders such as paronychia, dry skin/skin fissures, skin ulcer, and pruritus) may occur. Appropriate measures such as dose reduction or suspension of this drug should be taken. In addition, cases with complication of infection such as cellulitis and sepsis after occurrence of a severe skin disorder have been reported. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. Patients should be instructed to consult a dermatologist as necessary.

(2) Medical Devices

This section presents details of revisions to the Precautions section of package inserts of medical devices that have been revised in accordance with the Notification dated September 20, 2013.

1 Tracheostomy Masks (tracheal masks)

Warnings	When the misalignment of this product and the tracheostomy tube occur due to a patient movement or a fixation state, the connector port of the tracheostomy tube may be blocked, leading to dyspnea. Caution should be exercised and the use of this product should be considered taking into account these risks. In addition, when this product is used, a patient monitor should be concomitantly used according to the patient's condition.

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 October 1, 2013)

◎: Newly-posted products, or products changed from the last Bulletin

	Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
◎	Fentanyl Citrate E-fen buccal tablet 50 μg, 100 μg, 200 μg, 400 μg, 600 μg, 800 μg	Teikoku Seiyaku Co., Ltd.	September 26, 2013
◎	Norethisterone/Ethinylestradiol LUNABELL tablets ULD	Nobelpharma Co., Ltd.	September 26, 2013
◎	Aminolevulinic Acid Hydrochloride ALAGLIO Oral 1.5 g	SBI Pharmaceuticals Co., Ltd.	September 26, 2013
◎	Aminolevulinic Acid Hydrochloride Alabel Oral 1.5 g	Nobelpharma Co., Ltd.	September 18, 2013
◎	Lixisenatide Lyxumia Subcutaneous Injection 300 μg	Sanofi K.K.	September 17, 2013
◎	Tolvaptan Samsca tablets 7.5 mg*1	Otsuka Pharmaceutical Co., Ltd.	September 13, 2013
◎	Eculizumab (Genetical Recombination) Soliris Drip Infusion 300 mg*2	Alexion Pharma G.K.	September 13, 2013
◎	Pertuzumab (Genetical Recombination) PERJETA Intravenous Infusion 420 mg/14 mL	Chugai Pharmaceutical Co., Ltd.	September 12, 2013
◎	Bisoprolol Bisono tape 4 mg, 8 mg	Toa Eiyo Ltd.	September 10, 2013
◎	Irbesartan/Trichlormethiazide Irtra Combination Tablets LD, HD	Shionogi & Co., Ltd.	September 4, 2013
◎	Topiroxostat (1) TOPILORIC Tablets 20 mg, 40 mg, 60 mg (2) URIADEC Tab. 20 mg, 40 mg, 60 mg	(1) Fujiyakuhin Co., Ltd. (2) Sanwa Kagaku Kenkyusho CO., LTD.	September 4, 2013
	Ibandronate Sodium Hydrate Bonviva IV Injection 1 mg Syringe	Chugai Pharmaceutical Co., Ltd.	August 29, 2013
	Levetiracetam E Keppra Dry syrup 50%	UCB Japan Co. Ltd	August 29, 2013

	Abatacept (Genetical Recombination) ORENCIA SYRINGE FOR S.C. INJECTION 125 mg/1 mL	Bristol-Myers K.K.	August 27, 2013
	Hemin Normosang Infusion 250 mg	Orphan Pacific, Inc.	August 23, 2013
	Palivizumab (Genetical Recombination) Synagis for Intramuscular Injection 50 mg, 100 mg*3 Synagis Intramuscular Solution 50 mg, 100 mg*3	AbbVie G.K.	August 20, 2013
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*4	Novartis Pharma K.K.	August 20, 2013
	Omalizumab (Genetical Recombination) Xolair for s.c. injection 150 mg, 75 mg*5	Novartis Pharma K.K.	August 20, 2013
	Tofacitinib Citrate XELJANZ Tablets 5 mg	Pfizer Japan Inc.	July 30, 2013
	Metreleptin (Genetical Recombination) Metreleptin for Subcutaneous Injection 11.25 mg "SHIONOGI"	Shionogi & Co., Ltd.	July 25, 2013
	Saxagliptin Hydrate ONGLYZA Tablets 2.5 mg, 5 mg	Kyowa Hakko Kirin Co., Ltd.	July 9, 2013
	Oxybutynin Hydrochloride NEOXY TAPE 73.5 mg	Hisamitsu Pharmaceutical Co., Inc.	June 27, 2013
	Clofarabine Evoltra 20 mg I.V. Infusion	Sanofi K.K.	June 21, 2013
	Lidocaine Penles Tape 18 mg*6	Nitto Denko Corporation	June 14, 2013
	Tacrolimus Hydrate Prograf Capsules 0.5 mg, 1 mg*7	Astellas Pharma Inc.	June 14, 2013
	Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*8	Chugai Pharmaceutical Co., Ltd.	June 14, 2013
	Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg*9	Nippon Shinyaku Co., Ltd.	June 14, 2013
	Aripiprazole ABILIFY tablets 3 mg, 6 mg, 12 mg, ABILIFY OD tablets 3 mg, 6 mg, 12 mg, ABILIFY powder 1%, ABILIFY oral solution 0.1%*10	Otsuka Pharmaceutical Co., Ltd.	June 14, 2013
	Dexmedetomidine Hydrochloride (1) Precedex Intravenous Solution 200 μg "Hospira"*11 (2) PRECEDEX Intravenous Solution 200 μg "Maruishi"*11	(1) Hospira Japan Co., Ltd. (2) Maruishi Pharmaceutical Co., Ltd.	June 14, 2013
	Denosumab (Genetical Recombination) PRALIA SUBCUTANEOUS INJECTION 60 mg SYRINGE	Daiichi Sankyo Company, Limited	June 11, 2013
	Acotiamide Hydrochloride Hydrate Acofide Tablets 100 mg	Zeria Pharmaceutical Co., Ltd.	June 6, 2013
	Levetiracetam E Keppra Tablets 250 mg, 500 mg*12	UCB Japan Co. Ltd	May 31, 2013
	Istradefylline	Kyowa Hakko Kirin Co.,	May 30, 2013

	NOURIAST Tablets 20 mg	Ltd.	
	Rufinamide Inovelon Tablets 100 mg, 200 mg	Eisai Co., Ltd.	May 29, 2013
	Acamprosate Calcium Regtect Tablets 333 mg	Nippon Shinyaku Co., Ltd.	May 27, 2013
	Ofatumumab (Genetical Recombination) Arzerra for I.V. infusion 100 mg, 1000 mg	GlaxoSmithKline K.K.	May 24, 2013
	Tocilizumab (Genetical Recombination) ACTEMRA 162 mg Syringe for SC Injection, ACTEMRA 162 mg Auto-Injector for SC Injection	Chugai Pharmaceutical Co., Ltd.	May 24, 2013
	Exenatide BYDUREON for Subcutaneous Injection 2 mg	Astra Zeneca K.K.	May 16, 2013
	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Stribild Combination Tab.	Japan Tobacco Inc.	May 14, 2013
	Paromomycin Sulfate AMEPAROMO capsules 250 mg	Pfizer Japan Inc.	April 12, 2013
	Regorafenib Hydrate Stivarga tablets 40 mg*13	Bayer Yakuhin, Ltd.	March 25, 2013

*1 An additional indication for “fluid retention in patients with hepatic cirrhosis which is not adequately responded to other diuretics such as loop diuretics”

*2 An additional indication for “inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome”

*3 An additional indication for “prevention of serious lower respiratory tract disease caused by respiratory syncytial (RS) virus infection in neonates and infants aged ≤24 months with immunodeficiency or Down syndrome (early stage of an epidemic of RS viral infection)"

*4 An additional indication for “treatment of patients with macular oedema with retinal vein occlusion or choroidal neovascularization with pathologic myopia”

*5 An additional administration for “pediatrics”

*6 An additional indication for “relief of pain in laser irradiation treatment of the skin”

*7 An additional indication for “treatment of patients with interstitial pneumonia associated with polymyositis/dermatomyositis”

*8 An additional indication for “treatment of patients with malignant glioma”

*9 An additional indication for “analgesia of chronic pain cannot be managed by treatments with non-opioid analgesics”

*10 An additional indication for “treatment of patients with depression/depressive state (to be used only when the patient does not sufficiently respond to conventional therapy)”

*11 An additional indication for “sedation in surgery or treatment without intubation under local anesthesia”

*12 An additional administration for “pediatrics”

*13 EPPV was initiated in August 21, 2013 for an additional indication for “treatment of patients with gastrointestinal stromal tumour that has progressed after chemotherapy”