Pharmaceuticals and Medical Devices Safety Information

No. 283 September 2011

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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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No. 283 September 2011

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

AC	Doxorubicin and cyclophosphamide
ADRs	Adverse drug reactions
Afssaps	Agence française de sécurité sanitaire des produits de santé
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
aPTT	Activated partial thromboplastin time
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BALF	Bronchoalveolar lavage fluid
BE	Base excess
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BIPAP	Bilevel positive airway pressure
BUN	Blood urea nitrogen
CCr (CLcr)	Creatinine clearance
CD	Cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cl	Chloride
CNAMTS	Caisse Nationale d' Assurance Maladie des Travailleurs Salaries
Cr	Creatinine
CRP	C-reactive protein
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DIC	Disseminated intravascular coagulation
DLST	Drug lymphocyte stimulation test
DVT	Deep vein thrombosis
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPPV	Early Post-marketing Phase Vigilance
FDA	Food and Drug Administration
FDP	Fibrin degradation products
FSH	Follicle-stimulating hormone
FY	Fiscal year
hCG	human chorionic gonadotrophin
HCO_{3-}	Bicarbonate
HHV	Human herpesvirus
HIV	Human immunodeficiency virus
hMG	human menopausal gonadotrophin
HR	Hazard ratio
IgE	Immunoglobulin E
IL-2R	Interleukin-2 receptor
IU	International unit
JMDC	Japan Medical Data Center
K	Potassium
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
KPNC	Kaiser Permanente Northern California
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MP	Melphalan and prednisolone
MRI	Magnetic resonance imaging
M-VAC	A regimen consisting of methotrexate plus vinblastine, doxorubicin, and cisplatin
Na	Sodium
NRTI	Nucleoside reverse transcriptase inhibitor

$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2	Arterial oxygen partial pressure
pH	Hydrogen ion concentration
PLT	Platelet
PT-INR	Prothrombin time - international normalized ratio
RBC	Red blood cell count
R-CHOP	A regimen consisting of rituximab plus cyclophosphamide, doxorubicin,vincristine and prednisone
SaO_2	Arterial oxygen saturation
S.I.	Stimulation index
SNIIRAM	Système National d'Informations Inter Régimes de l'Assurance Maladie
SP-D	Surfactant protein D
TEN	Toxic epidermal necrolysis
U.S.	United States
WBC	White blood cell count
γ-GTP	Gamma-glutamyl transpeptidase

1

Safety Measures against Bladder Cancer Associated with Diabetes Medication "Pioglitazone Hydrochloride-Containing Products"

	Active ingredient	Brand Name (name of company)
Active ingredient Brand Name (name of company)	(1) Pioglitazone hydrochloride	(1) ACTOS Tablets 15, 30, ACTOS OD Tablets 15, 30 (Takeda Pharmaceutical Company Limited)
	(2) Pioglitazone hydrochloride/ glimepiride	(2) SONIAS Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
	(3) Pioglitazone hydrochloride/ metformin hydrochloride	(3) METACT Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
	(4) Pioglitazone hydrochloride/ alogliptin benzoate	(4) LIOVEL Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Antidiabetic agents	
Indications	(1) Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatments and may have insulin resistance: 1) a. Diet and exercise therapies alone b. Sulfonylurea along with diet and exercise therapies c. α-glucosidase inhibitor along with diet and exercise therapies d Biguanide along with diet and exercise therapies 2) Insulin along with diet and exercise therapies (2) Type 2 diabetes mellitus To be used only when the concomitant use of pioglitazone hydrochloride and glimepiride is considered appropriate. (3) Type 2 diabetes mellitus To be used only when the concomitant use of pioglitazone hydrochloride and metformin hydrochloride is considered appropriate. (4) Type 2 diabetes mellitus To be used only when the concomitant use of alogliptin benzoate and pioglitazone hydrochloride is considered appropriate.	

1. Introduction

Pioglitazone hydrochloride (hereinafter referred to as "pioglitazone") is an antidiabetic agent used to lower blood glucose by reducing insulin resistance, inhibiting glucose production in the liver, and promoting sugar utilization in the peripheral tissue. In Japan, 86 products (including generic drugs) containing pioglitazone as an active ingredient are approved as of July 2011 (brand names; ACTOS Tablets, ACTOS OD Tablets, SONIAS Combination Tablets, METACT Combination Tablets, and LIOVEL Combination Tablets, etc.).

ACTOS Tablets were approved in September 1999 in Japan. The manufacturing authorization holders (MAHs) estimate that the number of patients using ACTOS Tablets per year is approximately 1,320,000 (FY 2009). The total estimated number of patients using ACTOS Tablets, ACTOS OD

Tablets, and METACT Combination Tablets per year (from Feb.2010 to Jan.2011) is approximately 1.4 million (users of SONIAS Combination Tablets launched in June 2011 and LIOVEL Combination Tablets approved in July 2011 are not included).

On June 9, 2011, the French regulatory authority (Agence française de sécurité sanitaire des produits de santé [Afssaps]) issued a notification to suspend new prescriptions of medications containing pioglitazone as an active ingredient and to recommend patients currently being treated with the drug to consult their physicians based on an epidemiological study (Caisse Nationale d' Assurance Maladie des Travailleurs Salaries [CNAMTS] study) reported a possible risk of bladder cancer in patients treated with pioglitazone.[1)] In June 10, the Germany regulatory authority (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]) issued a similar restriction for use.[2)] The European Medicines Agency (EMA), however, has not suspended the use of pioglitazone and announced on June 9 that EMA will review this matter based on EU-wide discussions to determine appropriate actions.[3)]

Based on the above, MHLW reviewed the information about bladder cancer risk associated with pioglitazone reported in Japan and a newly reported study results including the CNAMTS study at the Subcommittee on Drug Safety of Committee on Drug Safety held on June 23, 2011. Accordingly, MHLW issued a notification on June 24 and required MAHs to revise the Precautions of the package inserts of their products.

PMDA has prepared an investigation report on this issue.[4)] The details are described below.

2. Review of the Bladder Cancer Risk in Japan and Overseas

(1) In Japan

MHLW has continued reviewing the necessity of safety measures against risk of bladder cancer associated with pioglitazone as needed based on the interim analysis reports, etc. from a study using the Kaiser Permanente Northern California (KPNC) database, which started in 2003 to evaluate the association between pioglitazone and bladder cancer in humans because a carcinogenicity study showed an increase of bladder tumors. In 2010, MHLW evaluated the necessity of additional safety measures based on the second interim analysis report, etc. from the KPNC cohort study and considered that it was difficult to make a conclusion about the association between pioglitazone and bladder cancer. However, the second analysis showed that bladder cancer risk increased in patients treated with pioglitazone and that the risk elevated with the duration of treatment and the cumulative dose of pioglitazone. Therefore, MHLW considered that it was and was moving on to take some safety measure to provide information to ensure the safe use of pioglitazone based on the data currently available, without waiting for the final report from the KPNC study that will come out in 2013.

(2) In France and Germany

In France, the Afssaps considered that the risks outweighed the benefits of pioglitazone based on the French CNAMTS study showing the increased bladder cancer risk in patients treated with pioglitazone compared to those not treated with pioglitazone. The Afssaps announced a suspension of new prescriptions of pioglitazone on June 9, 2011 and a product recall scheduled from July 11. Based on the recall order, the recall of pioglitazone-containing drugs from the French market started on July 11.

In Germany, a notification to suspend new prescriptions of pioglitazone was also issued on June 10. However, the BfArM recommended that patients currently being treated with pioglitazone not suspend their treatment before consulting with their physicians.

(3) In the EU

After the suspension of new prescriptions of pioglitazone in France, the EMA's Committee for Medicinal Products for Human Use (CHMP) was held from July 18 to 21. Based on the discussions at CHMP meetings, the EMA instructed the relevant manufacturers, while recognizing that pioglitazone

remains an important treatment option for patients with type 2 diabetes, to (1) include a description of patients with current bladder cancer or a history of bladder cancer or patients with uninvestigated macroscopic haematuria in the Contraindications sections in SmPC, (2) ensure periodic safety and efficacy evaluation, (3) evaluate the bladder cancer risk after administration of pioglitazone in an epidemiological study covering all of Europe to determine safety measures to minimize the risk based on the study outcome, (4) alert healthcare professionals in the Warnings section of SmPC to consider the risk factors (age, smoking status and exposure to specific chemical substances or procedures) in individual patients before starting pioglitazone, and (5) alert healthcare professionals in the Posology and method of administration section and the Warnings section of SmPC to start the treatment at a low dose in elderly patients since they are at high risk of bladder cancer as well as heart failure.[5)]

(4) In the U.S.

On June 15, 2011, the Food and Drug Administration (FDA) issued a Drug Safety Communication to inform healthcare professionals and patients of the following precautions on the potential increase of bladder cancer risk associated with the use of pioglitazone for more than one year based on the interim analysis report from the KPNC study.[6)] In the Communication, the FDA requires the MAHs to revise labeling and will continue its review of the KPNC and CNAMTS studies.

- Do not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.
- Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.
- Encourage patients to read the Medication Guide they get with their pioglitazone medicine.
- Report adverse events involving pioglitazone medicines to the FDA MedWatch program.

3. Investigation on the bladder cancer risk

(1) Summary of epidemiological studies, etc.

Data from 11 epidemiological studies, etc. were submitted by MAHs for the evaluation of the bladder cancer risk associated with pioglitazone. Out of these studies, two studies, which were mainly focused on the review by the FDA or the EMA, are summarized below.

1) KPNC study[7)]

The manufacturers-sponsored a 10-year observational cohort study that was conducted at the University of Pennsylvania in patients with diabetes aged 40 and above who are members of KPNC health plan. The cohort included 193,099 patients with diabetes. The study will be completed at the end of 2012, and the results will come out in 2013.

The 5-year interim analysis included 30,173 patients treated with pioglitazone and 162,926 patients not treated with pioglitazone. The median duration of treatment in patients treated with pioglitazone was 2 years. According to the data obtained between January 1997 and April 2008, 881 patients were newly diagnosed with bladder cancer (90 patients treated with pioglitazone and 791 patients not treated with pioglitazone). The primary analysis showed the hazard ratio (HR) for bladder cancer risk in patients treated with pioglitazone compared to those not treated with pioglitazone was 1.2 [95% confidence interval (CI), 0.9 - 1.5], suggesting no statistical significance. The results of stratified analysis are shown in the table below. After more than 24 months of treatment, the HR for bladder cancer risk in patients treated with pioglitazone against those not treated with pioglitazone was 1.4 (95% CI, 1.03 - 2.0).

Interim analysis for the KPNC study

	Median bladder cancer incidence (range) (100,000 person·years)	Age- and sex-adjusted HR (95% CI)	Adjusted HR* (95% CI)
Unexposed	68.8 (64.1 - 73.6)	Control	Control
Exposed***	81.5 (64.7 - 98.4)	1.2 (0.9 - 1.5)**	1.2 (0.9 - 1.5)
Time after starting pioglitazone***			
< 18 months	67.1 (41.8 - 92.4)	1.1 (0.8 - 1.6)	1.2 (0.8 - 1.7)
18 to 36 months	85.2 (51.8 - 118.6)	1.3 (0.9 - 2.0)	1.4 (0.9 - 2.1)
≥ 36 months	93.1 (63.5 - 122.7)	1.3 (0.9 - 1.8)	1.3 (0.9 - 1.8)
Test for trend		P=0.04	P=0.07
Duration of treatment with pioglitazone***			
< 12 months	48.4 (29.0 - 67.8)	0.8 (0.5 - 1.2)	0.8 (0.6 - 1.3)
12 to 24 months	86.7 (52.0 - 121.4)	1.3 (0.9 - 2.0)	1.4 (0.9 - 2.1)
≥ 24 months	102.8 (71.7 - 133.8)	1.5 (1.1 - 2.0)	1.4 (1.03 - 2.0)
Test for trend		P=0.02	P=0.03
Cumulative dose***			
1 to 10,500 mg	59.7 (39.0 - 80.4)	1.0 (0.7 - 1.4)	1.0 (0.7 - 1.5)
10,501 to 28,000 mg	76.8 (48.3 - 105.2)	1.1 (0.8 - 1.6)	1.2 (0.8 - 1.8)
≥ 28,000 mg	105.9 (68.0 - 143.8)	1.5 (1.1 - 2.2)	1.4 (0.96 - 2.1)
Test for trend		P=0.05	P=0.08

* All investigated potential confounding factors included in the analysis model
** Also adjusted for other antidiabetics
*** Patients not treated with pioglitazone used as the control for HR calculation

2) CNAMTS study[8)]

CNAMTS cohort study was conducted using the data collected between 2006 and 2009 on 1,491,060 diabetic patients (age of 40 to 79) registered with the Système National d'Informations Inter Régimes de l'Assurance Maladie (SNIIRAM) database in France. After adjusting for age, sex and use of other antidiabetics, it showed a significant increase of bladder cancer risk in patients treated with pioglitazone (175/155,535) compared with those not treated with pioglitazone (1,841/1,335,525) [HR, 1.22 (95% CI, 1.05 - 1.43)]. The bladder cancer risk significantly increased in patients treated with pioglitazone compared with those not treated when pioglitazone was used for 12 to 23 months [HR, 1.34 (95% CI, 1.02 - 1.75)], when it was used for 24 months ≤ [HR, 1.36 (95% CI, 1.04 - 1.79)] or when the cumulative dose was ≤ 28,000 mg [HR, 1.75 (95% CI; 1.22 - 2.50)].

(2) Adverse reaction reports in Japan

Among adverse reactions reported to the PMDA by July 15, 2011, those related to bladder cancer associated with products containing pioglitazone included 65 cases of bladder cancer, 2 cases of ureteric cancer, 2 cases of bladder neoplasm, and 1 case each of recurrent bladder cancer, bladder transitional cell carcinoma, and bladder squamous cell carcinoma. Stratified by year of onset of adverse reaction, 2 cases occurred in 2007, 4 cases in 2008, 5 cases in 2009, 17 cases in 2010 and 23 cases in 2011. Time of onset is unknown in 21 cases. All cases were reported after June 9, 2011 when the French authorities announced the suspension of pioglitazone use.

(3) Review based on the Japanese medical fee claim database

As a preliminary assessment, the risk of bladder cancer associated with pioglitazone was quantitatively evaluated using the available Japanese medical fee claim database. There were 9,909 diabetic patients and 296 bladder cancer patients. Of 31 patients with diabetes and bladder cancer, there are only 4 patients who had been newly diagnosed with bladder cancer after using pioglitazone.

Accordingly, a sufficient number of patients could not be obtained to allow appropriate evaluation of the bladder cancer risk.

This evaluation was based on data from approximately 480,000 members in the Japan Medical Data Center (JMDC) database (January 2005 to December 2009), which Japan Medical Data Center Co., Ltd. developed for secondary use of the information on health insurance claims collected from contracted multiple health insurance societies). Note that the database includes a smaller number of elderly people than that in the general Japanese population, and that it does not include claims made under the prospective payment system.

4. Review outcomes and safety measures

After the review including the interim analysis for the KPNC study and the data from the CNAMTS study, MHLW considered that it is appropriate to revise the Precautions section of the package insert and to alert healthcare professionals because, despite the limited interpretation of the study results, there is a possibility that the risk of bladder cancer in patients treated with pioglitazone may slightly increase with the duration of treatment. The risk may increase in patients treated with pioglitazone for more than one year, however, there is not enough evidence to limit treatment duration or cumulative dose. Therefore, MHLW concluded that no restriction of pioglitazone prescription (dose and treatment duration) is necessary.

On June 24, 2011, the MHLW issued a notification that required the MAHs to revise the "Precautions" section of package inserts of products containing pioglitazone. The revised precautions were also included in the package inserts of LIOVEL Combination Tablets approved on July 1 and generic drugs.[9)] In addition, all MAHs of products containing pioglitazone was required to alert healthcare professionals by preparing information materials for physicians to understand the bladder cancer risk and those for pharmacists to provide appropriate instructions about proper drug use to patients.

Important Precautions

Overseas epidemiological studies that included patients with diabetes suggested an increased risk of bladder cancer in patients taking pioglitazone. Some epidemiological study results also showed a tendency for a longer dosing period of pioglitazone to increase the risk of bladder cancer. Therefore, the following precautions are recommended (See the section of "Other Precautions"):

- Pioglitazone is not to be used in patients with active bladder cancer. The benefits and risks should be considered in patients with a prior history of bladder cancer to determine whether the drug should be administered.
- Patients or their families are to be given a full explanation of the risk of bladder cancer before initiating the therapy. Patients should be instructed to see their doctor immediately if they have any signs or symptoms of blood in the urine, pollakiuria or pain on urination during the treatment with this drug.
- Physicians should perform a urine test periodically during the treatment with this drug. If any abnormalities are observed, appropriate measures should be taken. Patients should also continue to be carefully monitored after the treatment with this drug.

Other Precautions

In an epidemiological study including patients with diabetes, the interim analysis showed no overall significant increase in the risk of bladder cancer with pioglitazone use (Hazard Ratio [HR] 1.2, 95% Confidence Interval [CI] 0.9 to 1.5). A stratified analysis, however, showed a significant increase of the bladder cancer risk in the duration of administration ≥2-year subgroup (HR 1.4 [95% CI 1.03-2.0]). In another epidemiological study, there was a statistically significant increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other anti-diabetic agents (HR 1.22; 95% CI 1.03 to 1.43). The results also showed a statistically significant increase of the bladder cancer risk for the duration of administration ≥1-year subgroup (HR 1.34; 95% CI 1.02 to 1.75)..

5. Future safety measures

After the regulatory notification issued on June 24, MHLW evaluated the necessity of additional safety measures in Japan based on the European regulatory announcement on July 21. MHLW considers that no new safety measures such as additional revision of package insert and discontinuation of pioglitazone use would be required at the moment as long as the safety measures described above are appropriately taken and the Precautions described in the package insert are complied with. Since no information on bladder cancer risk is available from Japanese patients, however, MHLW required the MAHs to continue to collect relevant information in Japan and overseas promptly, to provide it to healthcare professionals and patients, and to evaluate it to determine the necessity of new safety measures and investigations.

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8) http://www.afssaps.fr/content/download/34024/445581/version/1/file/RapportEtudeCNAMTS-Pioglitazonejuin-20113.pdf
9) http://www.info.pmda.go.jp/dsu/DSU201.pdf (only available in Japanese language)

2

Important Safety Information

This section presents the contents of revisions and case summaries that served as the basis for these revisions to important adverse reactions included under the Precautions section of package inserts of drugs that have been revised in accordance with the Notifications dated August 9 and 12, 2011.

1 Influenza HA Vaccine

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

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Vasculitis (allergic purpura, allergic granulomatous angiitis, leukocytoclastic vasculitis, etc.): Vasculitis (allergic purpura, allergic granulomatous angiitis, leukocytoclastic vasculitis, etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.

Oculomucocutaneous syndrome (Stevens-Johnson syndrome): Oculomucocutaneous syndrome may occur. Patients should be carefully monitored. 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, 2008 to March 31, 2011)

- Oculomucocutaneous syndrome (Stevens-Johnson syndrome): 1 case (no fatal cases)
- Vasculitis: 6 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 49,440,000 for seasonal influenza vaccines (FY 2010)

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	Female 60s	Influenza immunization (none)	0.5 mL Once	**Allergic granulomatous angiitis (Churg-Strauss syndrome)** The patient had bronchial asthma. Inhaled corticosteroid was used for bronchial asthma.

				She had histories of chronic eosinophilic pneumonia and chronic sinusitis. Eosinophilic pneumonia did not relapse from 9 years before vaccination. An increase in eosinophil count (10% - 20%) was noted from 7 months before vaccination, but without symptoms. She had pollen allergy. 18 days before vaccination: The patient received a seasonal influenza vaccination. 9 days before vaccination: Anorexia was noted. Other symptoms were not found. Day of vaccination: The patient received an influenza A (H1N1) vaccination. 3 days after vaccination: Purpura and redness developed in both legs. 4 days after vaccination: Numbness and pain in both legs developed, and she had difficulty walking. Eosinophils increased to more than 50%. Churg-Strauss syndrome was suspected. 5 days after vaccination: The patient was admitted to the hospital to have a detailed examination and treatment. 9 days after vaccination: Methylprednisolone sodium succinate for injection was administered at 1000 mg/day for 3 days. 12 days after vaccination: Oral administration of prednisolone was started at 60 mg. 41 days after vaccination: The dose of prednisolone was reduced to 55 mg. 48 days after vaccination: The dose of prednisolone was reduced to 50 mg. 62 days after vaccination: The dose of prednisolone was reduced to 45 mg. 76 days after vaccination: The dose of prednisolone was reduced to 40 mg. The outcome of Churg-Strauss syndrome was with sequelae (symptoms: peripheral neuropathy, multiplex mononeuritis).
	Concomitant medications: budesonide, montelukast sodium			

Laboratory Examination

	5 days after vaccination	7 days after vaccination	12 days after vaccination	20 days after vaccination	46 days after vaccination
Eosinophils (%)	54.5	56.0	0.0	0.5	0.0
WBC (/mm^3)	16170	15770	9960	7750	6910
PLT ($\times 10^4$/mm^3)	21.3	19.6	29.4	34.5	20.6
CRP (mg/dL)	1.8	4.2	0.2	0.1	0.1

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Influenza immunization (hypertension)	0.5 mL Once	**Oculomucocutaneous syndrome** Day of vaccination: The patient received an influenza HA vaccination. 1 day after vaccination:

				Swelling and pain in the left axilla developed. 2 days after vaccination: Rash all over the body, pyrexia at around 40°C, and mouth erosion were gradually noted and tended to become aggravated. Impaired eating ability and hallucination were noted. 4 days after vaccination: The patient visited Orthopedic Clinic A. Olopatadine hydrochloride and diclofenac sodium were prescribed, but there were no changes in the symptoms. 6 days after vaccination: The patient visited Internal Medicine Clinic B. Rickettsial infection was suspected, but the test result was negative. In the general biochemical test, abnormal hepatic function and high level of CRP were noted. Pyrexia at 39.6°C and rash on the extremities and trunk developed. The patient had redness and felt hot around the site of injection of vaccine on the left upper arm. 9 days after vaccination: The patient was referred and admitted to Hospital C because she had severe mouth erosion and irritating eye pain, and did not have meals. The patient was diagnosed with "oculomucocutaneous syndrome" by a doctor visiting from Dermatology Clinic D. • The dose of prednisolone was gradually reduced from 60 mg by 10 mg per time at intervals of 3 days (9 days - 29 days after vaccination). • Sulbactam sodium/ampicillin sodium 2 g/day for injection (9 days - 14 days after vaccination). • Monoammonium glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate 20 mL/day (9 days - 23 days after vaccination). • Famotidine injection solution 10 mg/day (9 days - 23 days after vaccination). 14 days after vaccination: Generalized rash (multiforme exudativum erythema) was alleviated and almost disappeared. Irritating eye pain also disappeared. Blood test 12 days after vaccination showed improvement of hepatic dysfunction. 24 days after vaccination: Oral mucous erosion was improved, and the patient was discharged from the hospital.
	Concomitant medications: valsartan, simvastatin			

Laboratory Examination

	6 days after vaccination	9 days after vaccination	12 days after vaccination	15 days after vaccination	23 days after vaccination
WBC (/mm^3)	11200	7050	9030	12010	9040
RBC (× 10$_4$/mm^3)	489	526	445	453	436
Hematocrit (%)	43.3	45.8	40.0	41.4	40.5
Hemoglobin (g/dL)	14.7	15.9	13.3	13.6	13.1
PLT (× 10^4/mm^3)	19.7	17.9	35.0	42.5	26.9
CRP (mg/dL)	14.39	10.91	2.54	0.75	0.12
AST (GOT) (IU/L)	52	48	23	18	11
ALT (GPT) (IU/L)	36	48	32	27	16
γ-GTP (IU/L)	37	-	-	-	-

LDH (IU/L)	246	279	180	187	113
Total bilirubin (mg/dL)	-	0.5	0.5	0.4	0.5
BUN (mg/dL)	16.1	22.9	13.6	20.2	18.4
Creatinine (mg/dL)	0.69	0.90	0.60	0.60	0.70
Na (mEq/L)	130	132	141	143	141
K (mEq/L)	4.1	3.6	3.8	4.4	4.2
Cl (mEq/L)	94	95	98	104	103

2 Thalidomide

Brand Name (name of company)	THALED CAPSULE 50, 100 (Fujimoto Pharmaceutical Corporation)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Relapsed or refractory multiple myeloma

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Deep vein thrombosis and pulmonary embolism may occur. This drug should be carefully administered by monitoring the patient's condition. If any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

Adverse Reactions (clinically significant adverse reactions)

Deep vein thrombosis, pulmonary embolism: Deep vein thrombosis or pulmonary embolism may occur or worsen. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Cerebral infarction: Cerebral infarction 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.

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.

Cardiac failure, arrhythmia: Cardiac failure (e.g., congestive cardiac failure), arrhythmia, bradycardia, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years (from initial marketing to June 17, 2011)

- Cerebral infarction: 4 cases (no fatal cases)
- Cardiac failure: 3 cases (no fatal cases)
- Interstitial pneumonia: 6 cases (no fatal cases)
- Pulmonary embolism: 3 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: Approximately 3,000 (August 1, 2010 to July 31, 2011)

Launched in Japan: February 2009 (THALED CAPSULE 100)
May 2010 (THALED CAPSULE 50)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Multiple myeloma (atrial fibrillation, spondylolisthesis, chronic renal failure, sick sinus syndrome, bronchial asthma, gastrointestinal haemorrhage)	100 mg for 13 days	**Pulmonary embolism** Approximately 1 year and 7 months before administration: The patient developed multiple myeloma. Approximately 2 months before administration: Melphalan and prednisolone (MP) therapy was performed (for approximately 1 month). Day 1 of administration: Administration of thalidomide was started at 100 mg/day. Day 11 of administration: The patient experienced deep vein thrombosis (DVT)-like symptoms and was admitted to the hospital. Day 12 of administration: The patient was diagnosed with DVT and pulmonary embolism based on a scan with contrast. Administration of heparin sodium was started. Day 13 of administration (day of discontinuation): Administration of thalidomide was discontinued. Administration of aspirin and warfarin potassium was started. 4 days after discontinuation: Symptoms remitted. As his symptoms were well-controlled with warfarin potassium, administration of aspirin and heparin sodium were discontinued, the patient was followed up with warfarin potassium.
	Concomitant medications: melphalan, prednisolone, sulfamethoxazole/trimethoprim, ambroxol hydrochloride, montelukast sodium, estazolam, senna leaf/senna fruit, rebamipide, lactomin, precpitated calcium carbonate, nicorandil, alfacalcidol, omeprazole, mecobalamin			

Laboratory Examination

	Day 11 of administration	Day 12 of administration	2 days after discontinuation	4 days after discontinuation	5 days after discontinuation
FDP (μg/mL)	44.3	-	14.3	-	12.6
D-dimer (μg/mL)	22.75	16.53	6.21	6.50	8.70

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Multiple myeloma (anxiety syndrome)	200 mg for 9 days	**Cerebral infarction** Approximately 4 months before administration: The patient was diagnosed with multiple myeloma. MP (melphalan 10 mg + prednisolone 30 mg for 4 days) therapy was performed once in 4 weeks. Day 1 of administration: Administration of thalidomide 200 mg and dexamethasone 40 mg was started. Day 5 of administration: Administration of dexamethasone was discontinued. Day 9 of administration (day of discontinuation): The patient went into a delirious state. Administration of thalidomide was discontinued. 4 days after discontinuation:

				Magnetic resonance imaging (MRI) showed cerebral infarction in the white matter of the left frontal lobe. Approximately 1.5 months after discontinuation: The patient recovered.
	Concomitant medications: dexamethasone			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 60s	Multiple myeloma (lumbar compression fracture)	50 mg for 7 days	**Drug-induced pneumonia (interstitial pneumonia)** Approximately 1 year and 5 months before administration: The patient developed multiple myeloma. Day 1 of administration: Administration of thalidomide was started at 50 mg. Day 5 of administration: The patient developed malaise. Day 7 of administration (day of discontinuation): The patient developed hyperthermia and discontinued thalidomide at her discretion. 1 day after discontinuation: Because the patient developed dyspnoea, she visited an emergency department and was urgently admitted to the hospital. The chest CT showed interstitial opacities (ground-glass opacities) in the whole lung field. No sign of cardiac failure was noted and the marker of interstitial pneumonia was elevated, and therefore the patient was diagnosed with interstitial pneumonia. After admission to the hospital, steroid pulse and bilevel positive airway pressure (BIPAP) were started for resuscitation, and post-steroid therapy were performed. During steroid pulse, drug lymphocyte stimulation test (DLST) was performed, and the test result was positive. 16 days after discontinuation: Oxygen therapy was discontinued, and the dose of the steroid was reduced. The patient was discharged from the hospital. 34 days after discontinuation: Symptoms remitted.
	Concomitant medications: none			

Laboratory Examination

	Day 1 of administration	2 days after discontinuation	3 days after discontinuation	8 days after discontinuation	71 days after discontinuation
LDH (IU/L)	191	674	796	687	406
KL-6 (U/mL)	-	-	576	3221	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Female 70s	Multiple myeloma (constipation, hypertension, numbness of limbs, diabetes mellitus,	100 mg for 22 days	**Aggravation of cardiac failure** [Medical history] cardiac failure, bigeminal pulse Approximately 1 year and 10 months before administration: The patient developed multiple myeloma. MP therapy was performed (for approximately 1 year and 3 months). Approximately 4 months before administration: High-dose dexamethasone was administered (for

		cardiac failure)		approximately 2 months). Approximately 3 months before administration: Bortezomib and dexamethasone was administered (for approximately 3 months). Day 1 of administration: Administration of thalidomide was started at 100 mg (The patient had cardiac failure as a complication). Day 13 of administration: The patient experienced extremities oedema, which was judged to be due to aggravation of cardiac failure based on an X-ray and his symptoms. Day 16 of administration: Administration of furosemide was started. Day 22 of administration (day of discontinuation): Administration of thalidomide was discontinued. 7 days after discontinuation: The patient was admitted to the hospital for treatment of oedema and cardiac failure. 87 days after discontinuation: Symptoms remitted.
	Concomitant medications: dihydroergotoxine mesilate, aspirin, amlodipine besilate, enalapril maleate, takadiastase/crude drug, carvedilol, benfotiamine/pyridoxine hydrochloride/cyanocobalamin, sodium gualenate hydrate/L-glutamine, tocopherol nicotinate, voglibose, cetirizine hydrochloride, clemastine fumarate, magnesium oxide, oxycodone hydrochloride hydrate, betamethasone butyrate propionate			

3 **Doxorubicin Hydrochloride** (non-liposome preparation)

Brand Name (name of company)	ADRIACIN Injection 10, 50 (Kyowa Hakko Kirin Co., Ltd.) Doxorubicin Hydrochloride Injection 10 mg [SANDOZ], 50 mg [SANDOZ] (Sandoz K.K.) Doxorubicin Hydrochloride for Injection 10 mg "NK", 50 mg "NK" (Nippon Kayaku Co., Ltd.)
Therapeutic Category	Antineoplastics-Antibiotics
Indications	◇ Conventional therapy with doxorubicin hydrochloride Remission of signs and symptoms of the following diseases: malignant lymphoma (reticulosarcoma, lymphosarcoma, Hodgkin's disease), lung cancer, gastrointestinal carcinoma (gastric cancer, gallbladder/bile duct cancer, pancreatic cancer, liver carcinoma, colon cancer, rectal cancer, etc.), breast cancer, bladder tumour, bone sarcoma Concomitant therapy with other anti-tumor agents for the following malignant tumors: Breast cancer (preoperative or postoperative chemotherapy for operable patients), corpus uteri carcinoma (postoperative chemotherapy, chemotherapy for metastasis/relapse), malignant bone and soft tissue tumor, malignant bone tumor, multiple myeloma, pediatric malignant solid tumor (Ewing's sarcoma family of tumor), rhabdomyosarcoma, neuroblastoma, retinoblastoma, hepatoblastoma, nephroblastoma, etc.) ◇ Methotrexate plus vinblastine, doxorubicin, and cisplatin (M-VAC) therapy Urothelial carcinoma

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

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.

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, 2008 to June 14, 2011)

- Interstitial pneumonia: No case

The number of patients using this drug per year estimated by MAHs: approximately 25,000 (2010)

Launched in Japan: March 1975 (ADRIACIN Injection 10)
November 2010 (ADRIACIN Injection 50)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Malignant lymphoma (hypertension, hyperlipidaemia, reflux oesophagitis, constipation, insomnia, left knee arthrosis)	72 mg/ 3 weeks (intravenous) 6 courses	**Interstitial pneumonia** 1 year and 9 months before administration: The patient was diagnosed with malignant lymphoma in the small intestine (follicular lymphoma, Stage I). 2 months before administration: With enlarged left axillary lymph nodes, malignant lymphoma in small intestine progressed to Stage IV. Day 1 of administration: Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy was started. Day 141 of administration: After the completion of 6 courses of R-CHOP, there was no finding of interstitial pneumonia on chest CT. Approximately 5 and a half months of administration: Dry cough occurred. Day 192 of administration: Soluble Interleukin-2 receptor (IL-2R, malignant lymphoma marker) elevated to 1590 U/mL. Day 203 of administration (day of onset): The patient was admitted to the hospital for a detailed examination. The patient had symptoms of exertional dyspnoea (shortness of breath, palpitations) at the time of admission. The chest X-ray showed ground-glass opacities in both lung fields. The chest CT showed diffuse ground-glass opacities and interstitial opacities, such as randomly-distributed small nodular shadows in the whole lung field. 2 days after onset: KL-6 1250 U/mL, SP-D 286 ng/mL, pH 7.409, BE 3.4 mEq/L, HCO_3^- 28.6 mEq/L, PaO_2 67.3 Torr, $PaCO_2$ 46.2 Torr, SaO_2 93.4%, body temperature 37.0°C 8 days after onset: Bronchoalveolar lavage fluid (BALF) (cell fractionation: lymphocytes 87%, macrophage 8%, Eosinophils 2%, Neutrophils 3%, CD4/CD8 = 0.2), result of culture in lung biopsy (negative).

				Lung biopsy showed finding of interstitial pneumonia associated with organising pneumonia. 22 days after onset: KL-6 1931 U/mL 30 days after onset: The patient was admitted to the respiratory department of another hospital, but had remission without treatment, and therefore the therapy including steroids was not performed. KL-6 1491 U/mL, pH 7.328, BE -0.9 mEq/L, HCO_{3-} 24.7 mEq/L, PaO_2 86.7 Torr, $PaCO_2$ 48.4 Torr, SaO_2 95.8%, body temperature 37.0°C. 32 days after onset: The patient was discharged from the hospital. DLST: negative for doxorubicin hydrochloride (Stimulation Index [S.I.], 94%), rituximab (genetical recombination) (S.I., 84%), cyclophosphamide hydrate (S.I., 125%), and vincristine sulfate (S.I., 175%).
	Concomitant medications: rituximab (genetical recombination) (suspected drug), cyclophosphamide hydrate (suspected drug), vincristine sulfate (suspected drug), prednisolone, granisetron hydrochloride, diphenhydramine hydrochloride, acetaminophen, amlodipine besilate, atorvastatin calcium hydrate, lansoprazole, sennoside A/B, etizolam, loxoprofen sodium hydrate			

Laboratory Examination

	Day 192 of administration	2 days after onset	19 days after onset	22 days after onset	30 days after onset
WBC (/mm^3)	3900	3400	2900	3400	3400
Eosinophil count (%)	5.2	4.8	5.2	3.5	2.6
CRP (mg/dL)	1.0	0.6	0.1	0.05	0.38
LDH (IU/L)	262	258	210	229	206
KL-6 (U/mL)	-	1250	-	1931	1491
Arterial blood pH	-	7.409	-	-	7.328
$PaCO_2$ (Torr)	-	46.2	-	-	48.4
PaO_2 (Torr)	-	67.3	-	-	86.7
HCO_{3-} (mEq/L)	-	28.6	-	-	24.7
SaO_2 (%)	-	93.4	-	-	95.8

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Breast cancer (diabetes mellitus)	93 mg/ 3 weeks (intravenous) for 4 courses	**Interstitial pneumonia** Day 1 of administration: The patient started receiving doxorubicin hydrochloride and cyclophosphamide hydrate as adjuvant chemotherapy after surgery for breast cancer. Approximately 3 weeks of administration: The patient complained of some breathing difficulty from around the 2nd course, but a lung examination, etc was not performed, and doxorubicin and cyclophosphamide (AC) therapy was continued until the 4th course. Day 81 of administration (day of onset): Dyspnoea occurred. A chest X-ray and CT were performed. Bilateral diffuse ground-glass opacities were noted. The patient was diagnosed with interstitial pneumonia and referred to the department of respiratory medicine. KL-6 382 U/mL, Sp-D 176 ng/mL

				Treatment was started at the department of respiratory medicine. To maintain SpO_2 of 90%, oxygen inhalation was started from 2 L (room air), and was increased up to 4 L (room air) at night. 1 day after onset: Administration of sulfamethoxazole/trimethoprim was started. 2 days after onset: Because breathing difficulty further worsened, the dose of oxygen inhalation was increased to 6 L (room air). Administration of meropenem hydrate and steroid pulse therapy (methylprednisolone sodium succinate 1000 mg) were started. After that, dyspnoea gradually remitted. 5 days after onset: Pneumonia-causing bacteria, carinii pneumonia, etc. were not detected, and therefore administration of antibiotics was discontinued. Administration of prednisolone sodium succinate 60 mg (drip infusion) was started. The dose of prednisolone sodium succinate was gradually reduced (60 mg - 10 mg). 34 days after onset: The patient recovered from interstitial pneumonia. KL-6 453 U/mL, Sp-D 29.6 ng/mL 37 days after onset: The patient was discharged from the hospital.
	Concomitant medications: cyclophosphamide hydrate (suspected drug)			

Laboratory Examination

	Day 81 of administration (day of onset)	3 days after onset	10 days after onset	13 days after onset	20 days after onset	34 days after onset
WBC (/mm^3)	2800	4400	7000	7200	8600	6500
Eosinophil count (%)	0.7	0.0	4.3	9.7	1.3	2.8
CRP (mg/dL)	5.89	7.21	0.17	1.19	0.13	-
LDH (IU/L)	576	735	251	271	256	199
KL-6 (U/mL)	382	-	-	-	-	453
Sp-D (ng/mL)	176.0	-	-	-	-	29.6
β-D-glucan (pg/mL)	3.8>	-	-	-	-	-

4 Dabigatran Etexilate Methanesulfonate

Brand Name (name of company)	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Anticoagulants
Indications	Suppression of development of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

PRECAUTIONS (underlined parts are revised)

Warnings

WARNINGS

Some fatal cases associated with haemorrahge such as gastrointestinal haemorrhage were confirmed after administration of this drug. When administrating this drug, use of this drug should be carefully determined based on risk of haemorrhage.

Any index which enables accurate evaluation of the risk of haemorrhage associated with this drug has not been established, and there is no drug to neutralize the anticoagulant action of this drug. Patients should be carefully monitored for signs of haemorrhage or anaemia as with test results related to blood coagulation during the administration of this drug. If these signs are observed, appropriate measures should be taken immediately.

Precautions of Dosage and Administration

(1) The blood concentration of dabigatran may increase in the following patients. This drug should be carefully administered, considering the dosage of this drug, 110 mg twice a day.

- Patients with moderate renal disorder (creatinine clearance 30 - 50 mL/min)
- Patients treated with concomitant P-glycoprotein inhibitor (oral dosage form)

(2) In the following patients who are considered to be at a high risk of haemorrhage, this drug should be carefully administered, considering the dosage of this drug, 110 mg twice a day.

- Patients aged 70 and older
- Patients with a history of gastrointestinal haemorrhage

Careful Administration

Patients treated with concomitant P-glycoprotein inhibitor (oral dosage form)

Important Precautions

When administrating this drug, use of this drug should be carefully determined based on risk of haemorrhage due to the patient's condition (renal function, elderly, history of gastrointestinal haemorrhage, etc.).

Any index which enables accurate evaluation of the risk of haemorrhage associated with this drug has not been established. Patients should be carefully monitored for signs of haemorrhage or anaemia, etc. as with test results related to blood coagulation during the administration of this drug. If these signs are observed, appropriate measures, including discontinuation of administration and haemostasis, should be taken immediately. Special attention should be paid to the patients described in the section of "Careful Administration."

It should be noted that haemorrhage may occur at any site during administration of this drug. Attention should be paid to any signs of haemorrhage including decreases in haemoglobin, haematocrit, and blood pressure, or haematuria. Special attention should be paid to gastrointestinal haemorrhage. If any symptoms such as haematemesis and bloody stool are observed, administration should be discontinued.

This drug is mainly excreted via the kidneys. Therefore, in patients with renal disorder, the blood concentration of this drug may increase, leading to increased risk of haemorrhage. Before administration of this drug, renal function must be checked.

In addition, during administration of this drug, the renal function test should be performed as necessary. If renal function is aggravated, discontinuation of administration or dose reduction should be considered.

Patients should be thoroughly informed that haemorrhage is likely to occur. They should be instructed to immediately contact their physician if any abnormal haemorrhage including epistaxis, gingival bleeding, subcutaneous haemorrhage, haematuria, and bloody stool are observed.

Adverse Reactions (clinically significant adverse reactions)

Haemorrhage (gastrointestinal haemorrhage, intracranial haemorrhage, etc): Haemorrhage such as gastrointestinal haemorrhage, intracranial haemorrhage may occur. Patients should be carefully monitored, and if such symptoms 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 5 months (from initial marketing to August 11, 2011)

- Haemorrhage: 5 cases (5 fatal cases)

The number of patients using this drug estimated by MAHs: Approximately 64,000 (July 2011)

Launched in Japan: March 2011

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Atrial fibrillation (hepatitis C, diabetes mellitus, renal failure, hypertension, angina pectoris, cardiac failure)	220 mg for 15 days	**Pulmonary alveolar haemorrhage, respiratory failure, epistaxis, haemoptysis, anaemia, haematuria, melaena** Body height: 154 cm, Body weight: 38.9 kg Approximately 3 years before administration: The patient started receiving warfarin potassium (1 mg/day) as anticoagulant therapy for atrial fibrillation. 50 days before administration: Cr 2.21 mg/dL, CCr 12 mL/min (calculation: Cockcroft-Gault method) 14 days before administration: Administration of warfarin potassium was discontinued due to inadequate response. Day 1 of administration: Administration of dabigatran etexilate methanesulfonate was started. Around Day 12 of administration: Bloody sputum and epistaxis were noted. Day 15 of administration (day of discontinuation): Bloody sputum and dyspnoea were noted. The patient experienced bleeding tendency and was transported to the emergency outpatient department of another hospital. The patient was admitted to the hospital in the evening for a detailed examination. At the hospital visit, haematuria, pulmonary alveolar haemorrhage, worsening of bloody sputum, respiratory failure, and tarry stool were noted. The patient was diagnosed with bilateral pneumonia, type I respiratory failure, and anaemia. Drip infusion of antibiotic, fluid replacement, drip infusion of haemostatics, and administration of oxygen were started. Oral administration of dabigatran etexilate methanesulfonate was discontinued. aPTT > 80 sec., Cr 4.2 mg/dL, eGFR 7 mL/min/ 1.73 m^2 After 1 hour and 30 minutes, wheezing became prominent, bloody sputum persisted, and haemoptysis was noted. After approximately 1 hour and 50 minutes, 4 units of fresh frozen plasma and menatetrenone 20 mg were intravenously administered. After 4 hours and 20 minutes, 2 units of red blood cell transfusion was performed. After approximately 5 hours, massive tarry stool was noted. After 7 hours, PT-INR was 7.51, and massive bloody sputum, tarry stool, and haematuria persisted. 1 day after discontinuation: Early in the morning, 2 units of red blood cell transfusion was

				performed. Administration of oxygen (using reservoir mask) 10 L/min was started. After approximately 1 hour and 20 minutes, heart rate decreased. After 1 hour and 35 minutes, death was confirmed.
	Concomitant medications: digoxin, losartan potassium, diltiazem hydrochloride, miglitol, ursodeoxycholic acid, furosemide, itopride hydrochloride, combination drug containing clostridium butyricum.			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 80s	Atrial fibrillation (femoral neck fracture, melaena, deep vein thrombosis, hypertension, hepatitis C, angina pectoris, renal disorder, pleural effusion)	220 mg for 7 days	**Exsanguination, increased international normalised ratio (INR), melaena** Body height: 163 cm, Body weight: 53 kg 22 days before administration: The patient was admitted to the hospital due to femoral neck fracture. 21 days before administration: Femoral neck prosthetic replacement was performed (general anaesthesia). 19 days before administration: As anaemia progressed, upper gastrointestinal tract endoscopy was performed, which showed an elevated lesion in the gastric corpus. However, haemorrhage was not noted. Anaemia was treated with packed red blood cell transfusion. 18 days before administration: Atrial fibrillation developed at night. 17 days before administration: Administration of digoxin (0.125 mg/day) was started for atrial fibrillation (for 4 days). 14 days before administration: Administration of aspirin (100 mg/day) was started (for 11 days). 13 days before administration: Lower-limb vascular echo showed deep vein thrombosis, and administration of warfarin potassium (3 mg/day) was started. 11 days before administration: Since PT-INR increased to 4.4, warfarin potassium was suspended. 10 days before administration: PT-INR increased, menatetrenone was administered. PT-INR 5.39 9 days before administration: Administration of warfarin potassium (1.5 mg/day) was resumed. PT-INR 1.49 8 days before administration: PT-INR was 2.32. The dose of warfarin potassium (1 mg/day) was reduced. 4 days before administration: Melaena was noted. Administration of warfarin potassium and aspirin was discontinued. PT-INR 2.6 3 days before administration: Cr 1.15 mg/dL, CCr 29 mL/min (calculation: Cockcroft-Gault method) 2 days before administration: The dose of warfarin potassium was reduced (0.5 mg/day), and

				administration was resumed. 1 day before administration: Stool became normalized, with no finding of gastrointestinal haemorrhage. Administration of warfarin potassium was discontinued. Date unknown: eGFR was 32.9 mL/min/1.73 m^2 immediately before administration of dabigatran etexilate methanesulfonate. Day 1 of administration: PT-INR was 1.35, administration of dabigatran etexilate methanesulfonate (110 mg × 2/day) was started. aPTT 43.4 sec. Day 4 of administration: Bloodstained faeces was noted at night. Because the amount of blood was very small, follow-up observation was performed. A test for melaena was not performed. Day 5 of administration: aPTT 71.7 sec. Day 7 of administration (day of discontinuation): Bloodstained faeces was noted again. Vital signs showed no problems. Administration of dabigatran etexilate methanesulfonate was discontinued. 1 day after discontinuation: Dark brown bloody stool was noted. PT-INR further increased to 2.33. aPTT 74.6 sec. 3 days after discontinuation: Melaena was confirmed. Hemoglobin decreased to the 7 g/dL level. Packed red blood cell transfusion was performed. aPTT 75.6 sec. 4 days after discontinuation: Melaena was confirmed. Melaena increased to approximately 200 g per time. The dose of transfusion was increased, and the patient underwent a follow-up observation, but melaena further increased. Despite blood transfusion, melaena persisted. 5 days after discontinuation: Early in the morning, massive bleeding was noted, and subsequently the patient went into a state of shock, resulting in cardiac arrest. Cardiopulmonary resuscitation was performed, but the patient did not regain consciousness. After approximately 40 minutes, cardiac arrest persisted, and death was confirmed. Autopsy: not performed. Cause of death: bleeding to death due to gastrointestinal haemorrhage.
	Concomitant medications: omeprazole, nicorandil, spironolactone, furosemide, limaprost alfadex, ursodeoxycholic acid, digoxin, amino acid/glucose/electrolytes/vitamins			

3

Revision of Precautions (No. 229)

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 August 9, 2011 (excluding those presented in 2. Important Safety Information of this Bulletin).

1 Psychotropics

Modafinil

Brand Name	MODIODAL Tablets 100 mg (Alfresa Pharma Corporation)
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: These disorders 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. **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. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged, and thus caution should be exercised. **Shock, anaphylactoid symptoms**: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored, and if any abnormalities including urticaria, pruritus, angioedema, dyspnoea, decreased blood pressure, and cyanosis are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference Information	Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

2 Kampo medicines

Shakuyakukanzoto

Brand Name	TSUMURA Shakuyakukanzoto Extract Granules for Ethical Use (Tsumura & Co. and others)
Adverse Reactions (clinically significant adverse reactions)	**Interstitial pneumonia**: If cough, dyspnoea, pyrexia, or abnormal chest sound are observed, administration of this drug should be discontinued, examinations including chest X-ray and chest CT scan should be performed immediately, and appropriate measures including administration of corticosteroids should be taken.

3

Antiarrhythmic agents

Esmolol Hydrochloride

Brand Name

BREVIBLOC inj. 100 mg (Maruishi Pharmaceutical Co., Ltd.)

Adverse Reactions (clinically significant adverse reactions)

Cardiac failure, peripheral ischaemia: If these symptoms occur, appropriate measures such as dose reduction or discontinuing administration should be taken. **Cardiac arrest, severe bradycardia**, and **atrioventricular block**: These symptoms may occur. If any abnormalities are observed, appropriate measures such as discontinuation of this drug should be taken.

4

Cardiovascular agents-Miscellaneous

Bosentan Hydrate

Brand Name

Tracleer Tablet 62.5 mg (Actelion Pharmaceuticals Japan Ltd.)

Important Precautions

Decreased haemoglobin, thrombocytopenia, etc. may occur in association with administration of this drug. A blood test should be performed at the start of administration, every month in the first 4 months and once every 3 months thereafter.

Adverse Reactions (clinically significant adverse reactions)

Pancytopenia, leukopenia, neutropenia, thrombocytopenia, anaemia: Pancytopenia, leukopenia, neutropenia, thrombocytopenia, or anaemia (decreased haemoglobin) may occur. Patients should be carefully monitored through periodic blood tests, and if any abnormalities are observed, appropriate measures, such as dose reduction and discontinuing administration, should be taken.

5

Hormones-Miscellaneous

Clomifene Citrate

Brand Name

Clomid Tablet 50 mg (Shionogi & Co., Ltd. and others)

Adverse Reactions (clinically significant adverse reactions)

Ovarian hyperstimulation syndrome: When this drug is administered, and when follicle-stimulating hormone (FSH), human menopausal gonadotrophin (hMG), human chorionic gonadotrophin (hCG) are used following administration of this drug or concomitantly with this drug, ovarian hyperstimulation syndrome with ovarian enlargement, torsion of ovary, lower abdominal pain, tense feeling of lower abdomen, and retention of ascites or pleural effusion may occur. Haemoconcentration, increased blood coagulation, dyspnoea, etc. may concurrently occur. In such case, administration of this drug should be discontinued immediately, and appropriate measures, such as making efforts for improvement of volume blood, should be taken.

6

Miscellaneous metabolism agents and antimetabolites

Methotrexate

Brand Name

METHOTREXATE PARENTERAL 5 mg, 50 mg, METHOTREXATE INJECTION 200 mg, METHOTREXATE TABLETS 2.5 mg, RHEUMATREX CAPSULES 2 mg (Pfizer Japan Inc. and others)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia, pulmonary fibrosis, pleural effusion: Interstitial pneumonia, pulmonary fibrosis, pleural effusion, etc. may occur, resulting in respiratory failure. Patients should be carefully monitored, and if pyrexia and any respiratory symptoms such as cough and dyspnoea are observed, examinations including a chest X-ray should be performed immediately, administration of this

drug should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

7 Acting mainly on gram-positive bacteria and mycoplasma

Azithromycin Hydrate (Tablets 250 mg, 600 mg, capsules for pediatric, fine granules for pediatric, injectable dosage form)

Brand Name	ZITHROMAC Tablets 250 mg, 600 mg, ZITHROMAC Capsules for Pediatric Use 100 mg, ZITHROMAC Fine Granules for Pediatric Use 10%, ZITHROMAC Intravenous use 500 mg (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Pseudomembranous colitis, haemorrhagic colitis**: Serious colitis including pseudomembranous colitis and haemorrhagic colitis may occur. If abdominal pain, frequent diarrhoea, bloody stool, etc. are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

8 Acting mainly on gram-positive bacteria and mycoplasma

Azithromycin Hydrate (dry syrup for adult)

Brand Name	ZITHROMAC SR Dry Syrup 2 g (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Pseudomembranous colitis, haemorrhagic colitis**: Serious colitis including pseudomembranous colitis and haemorrhagic colitis may occur. If abdominal pain, frequent diarrhoea, bloody stool, etc. are observed, appropriate measures should be taken.

9 Acting mainly on gram-positive bacteria and mycoplasma

Clarithromycin

Brand Name	KLARICID TABLETS 200 mg, KLARICID SYRUP FOR PEDIATRIC USE, KLARICID TABLETS 50 mg FOR PEDIATRIC USE (Abbott Japan Co., Ltd.), Clarith tab. 200, Clarith tab. 50 for pediatric, Clarith dry syrup 10% for pediatric (Taisho Pharmaceutical Co., Ltd. and others)
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 swollen lymph nodes, hepatic dysfunction, leukocytosis, eosinophilia, and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised. **Acute renal failure, tubulointerstitial nephritis**: Acute renal failure and tubulointerstitial nephritis may occur. Patients should be carefully monitored. If any symptoms such as oliguria or any findings of decreased kidney function such as increased blood creatinine level are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference Information	Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

10 **Antibiotics-Miscellaneous**

Lansoprazole/Amoxicillin Hydrate/Clarithromycin

Brand Name	LANSAP 400, 800 (Takeda Pharmaceutical Company Limited)
Adverse Reactions (clinically significant adverse reactions)	(Clarithromycin) **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. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised. **Acute renal failure, tubulointerstitial nephritis**: Acute renal failure and tubulointerstitial nephritis may occur. Patients should be carefully monitored. If any symptoms such as oliguria or any findings of decreased kidney function such as increased blood creatinine level are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference Information	Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

11 **Synthetic antibacterials**

Ofloxacin (oral dosage form)

Brand Name	TARIVID TABLETS 100 mg (Daiichi Sankyo Company, Limited. and others)
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including Torsades de pointes)** **Fulminant hepatitis, hepatic dysfunction, jaundice** (Initial symptoms: queasy/vomiting, anorexia, malaise, itching, etc.)

12 **Synthetic antibacterials**

Levofloxacin Hydrate (oral dosage form) (low-dose)

Brand Name	Levofloxacin Tablets 100 mg "KAKEN" (Shiono Chemical Co., Ltd. and others)
Adverse Reactions (clinically significant adverse reactions)	**Prolonged QT, ventricular tachycardia (including Torsades de pointes)**

13 **Synthetic antibacterials**

Levofloxacin Hydrate (oral dosage form) (high-dose)
Levofloxacin Hydrate (injectable dosage form)

Brand Name	CRAVIT TABLETS 250 mg, 500 mg, CRAVIT FINE GRANULES 10% (Daiichi Sankyo Company, Limited) CRAVIT INTRAVENOUS DRIP INFUSION BAG 500 mg/100 mL, CRAVIT INTRAVENOUS DRIP INFUSION 500 mg/20 mL (Daiichi Sankyo Company, Limited)
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.

14 Antivirals

Maraviroc

Brand Name

CELSENTRI Tablets 150 mg (ViiV Healthcare K.K.)

Precautions of Indications

"To be used only when the patient does not sufficiently respond to other anti-HIV drugs or when the patient is considered to have poor tolerability."
The sentence, "The safety and efficacy have not been established in anti-HIV drug treatment-naive HIV-1 infected adults and HIV-1-infected children." was deleted.
The efficacy and safety of this drug have not been established in HIV-1-infected children.

Precautions of Dosage and Administration

The efficacy and safety have not been established at dosage beyond 300 mg twice daily (no experience of administration).

Concomitant medications	Dose of this drug
Tipranavir/ritonavir, nevirapine, raltegravir, and all other concomitant medications including nucleoside reverse transcriptase inhibitors (NRTI) and enfuvirtide	300 mg twice daily

In patients with renal impairment (CLcr < 80 mL/min) treated with a potent CYP3A4-inhibitor, this drug should be administered depending on the status of decreased renal function based on the following dosing intervals and doses. However, the efficacy and safety have not been established for the adjustment of these dosing intervals. Patients should be carefully monitored for changes in their clinical symptoms, etc. (Based on data in non-Japanese)

Concomitant medications	Creatinine clearance < 80 mL/min
In case of not concomitantly using a potent CYP3A4 inhibitor or in case of concomitantly using tipranavir/ritonavir	Adjustment of dosing intervals is not needed. (300 mg every 12 hours)
In case of concomitantly using fosamprenavir/ritonavir	150 mg every 12 hours
In case of concomitantly using a potent CYP3A4 inhibitor: In case of concomitantly using saquinavir/ritonavir lopinavir/ritonavir, darunavir/ritonavir atazanavir/ritonavir, ketoconazole, etc.	150 mg every 24 hours

Important Precautions

In a clinical study conducted in healthy adult volunteers, 1 case of hepatic disorder associated with an allergic symptom suspected to be caused by this drug has been reported. In addition, in a clinical study conducted in HIV-infected patients regardless of past treatment, increases of abnormal liver function test and hepatic disorder have been reported, but increases of Grades 3 or 4 abnormal liver function test were not confirmed. If hepatitis or any systemic allergic symptom (pruritic rash, eosinophilia, increased IgE, etc.) is observed after administration of this drug, appropriate measures such as discontinuing administration should be taken.
If boosted this drug and a protease inhibitor are concomitantly used in patients with severe renal impairment, the blood concentration of this drug may increase, leading to an increased risk of orthostatic hypotension. Patients should be carefully monitored for changes in their clinical symptoms, etc. Special attention should be paid when concomitantly using a protease inhibitor, which has a potent CYP3A4 inhibitory action.

Adverse Reactions (clinically significant adverse reactions)	Oculomucocutaneous syndrome (Stevens-Johnson syndrome)

15 **Chemotherapeutics-Miscellaneous, Antiprotozoans**

Sulfamethoxazole/Trimethoprim

Brand Name	Baktar Combination Tablets, Baktar Combination Granules (Shionogi & Co., Ltd.), BACTRAMIN Combination Tablet, BACTRAMIN Combination Granule, BACTRAMIN Injection (Chugai Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome**: Rash and pyrexia may occur as the initial symptoms followed by hepatic dysfunction and serious late-onset hypersensitivity symptoms with swollen lymph nodes, leukocytosis, eosinophilia, and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. The reactivation of viruses including 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	Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reactions: Drug-Induced Hypersensitivity Syndrome

16 **Human blood preparations**

Eptacog Alfa (Activated) (Genetical Recombination)

Brand Name	NovoSeven for Injection 1.2 mg, 4.8 mg, NovoSeven HI for Injection 1 mg, 2 mg, 5 mg (Novo Nordisk Pharma Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Thromboembolism**: arterial thromboembolism (myocardial infarction, cerebral infarction, intestinal ischaemia, etc.) and venous thromboembolism (pulmonary embolism, thrombophlebitis, deep vein thrombosis, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken. **Disseminated intravascular coagulation (DIC)**: Disseminated intravascular coagulation (DIC) may occur. Patients should be carefully monitored. If any abnormal coagulation test values including decreases in platelet count or fibrinogen level and increases in FDP or D-dimer are observed, appropriate measures should be taken.

17 **Over-the-counter drugs**

Shakuyakukanzoto

Brand Name	Tsumura Kampo Shakuyakukanzoto Extract Granules (Tsumura & Co.)
Consultation	If you experience any of the following symptoms after taking the product, immediately discontinue the use of the product, and show this document to your physician or pharmacist for consultation. The following serious symptoms occur in rare cases. In such cases, immediately seek medical aid. **Interstitial pneumonia**: Shortness of breath, dyspnoea, and pyrexia, etc. may occur together with cough.

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 September 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Azacitidine Vidaza for Injection 100 mg	Nippon Shinyaku Co., Ltd.	March 11, 2011
Fondaparinux Sodium Arixtra Injection 5 mg, 7.5 mg	GlaxoSmithKline K.K.	March 11, 2011
Ustekinumab (Genetical Recombination) Stelara Subcutaneous Injection 45 mg Syringe	Janssen Pharmaceutical K.K.	March 14, 2011
Dabigatran Etexilate Methanesulfonate Prazaxa Capsules 75 mg, 110 mg	Nippon Boehringer Ingelheim Co., Ltd.	March 14, 2011
Galantamine Hydrobromide REMINYL Tablets 4 mg, 8 mg, 12 mg, REMINYL OD Tablets 4 mg, 8 mg, 12 mg, REMINYL Oral Solution 4 mg/mL	Janssen Pharmaceutical K.K.	March 22, 2011
Eldecalcitol EDIROL Capsule 0.5 μg, 0.75 μg	Chugai Pharmaceutical Co., Ltd.	April 11, 2011
Freeze-dried, Cell Culture-Derived Japanese Encephalitis Vaccine (Inactivated) ENCEVAC Subcutaneous Injection	The Chemo-Sero-Therapeutic Research Institute	April 11, 2011
Romiplostim (Genetical Recombination) Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Ltd.	April 13, 2011
Anti-human Thymocyte Immunoglobulin, Rabbit Thymoglobuline for Intravenous Infusion 25 mg*[1]	Genzyme Japan K.K.	April 22, 2011
Doripenem Hydrate FINIBAX for Drip Infusion 0.25 g, FINIBAX Kit for Drip Infusion 0.25 g*[2]	Shionogi & Co., Ltd.	April 22, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.25% inj. 25 mg/10mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL*[3]	Maruishi Pharmaceutical Co., Ltd.	April 22, 2011
Repaglinide SUREPOST Tablets 0.25 mg, 0.5 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 16, 2011
Febuxostat Feburic Tablet 10 mg, 20 mg, 40 mg	Teijin Pharma Limited	May 17, 2011

Levonorgestrel NORLEVO 0.75 mg Tablet	Sosei Co. Ltd.	May 24, 2011
Pioglitazone Hydrochloride/Glimepiride SONIAS Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	June 6, 2011
Memantine Hydrochloride MEMARY TABLETS 5 mg, 10 mg, 20 mg	Daiichi Sankyo Company, Limited	June 8, 2011
Adalimumab (Genetical Recombination) HUMIRA for s.c. injection syringe 40 mg/0.8 mL, HUMIRA for s.c. injection syringe 20 mg/0.4 mL*[4]	Abbott Japan Co., Ltd.	July 1, 2011
Erlotinib Hydrochloride TARCEVA Tablets 25 mg, 100 mg*[5]	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Gabapentin GABAPEN Tablets 200 mg, 300 mg, 400 mg*[6]	Pizer Japan Inc.	July 1, 2011
Peginterferon Alfa-2a (Genetical Recombination) PEGASYS s.c. 90 μg, 180 μg*[7]	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Lamotrigine Lamictal Tablets 25 mg, 100 mg*[8]	GlaxoSmithKline K.K.	July 1, 2011
Ribavirin COPEGUS Tablet 200 mg*[9]	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Edoxaban Tosilate Hydrate LIXIANA TABLETS 15 mg, 30 mg	Daiichi Sankyo Company, Limited	July 19, 2011
Eribulin Mesilate Halaven injection 1 mg	Eisai Co., Ltd.	July 19, 2011
Tramadol Hydrochloride/Acetaminophen TRAMCET Combination Tablets	Janssen Pharmaceutical K.K.	July 19, 2011
Rivastigmine EXELON PATCH 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis Pharma K.K.	July 19, 2011
Rivastigmine RIVASTACH Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharmaceutical Co., Ltd.	July 19, 2011
Epoetin Beta Pegol (Genetical Recombination) MIRCERA Injection Syringe 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg	Chugai Pharmaceutical Co., Ltd.	July 20, 2011
Pramipexole Hydrochloride Hydrate Mirapex-LA Tablets 0.375 mg, 1.5 mg	Nippon Boehringer Ingelheim Co., Ltd.	July 20, 2011
Mitiglinide Calcium Hydrate/Voglibose GLUBES Combination Tab.	Kissei Pharmaceutical Co., Ltd.	July 22, 2011
Desflurane Suprane Inhalational Anesthetic Solution	Baxter Limited	July 29, 2011
Buprenorphine NORSPAN TAPE 5 mg, 10 mg, 20 mg	Mundipharma K.K.	August 4, 2011
Escitalopram Oxalate LEXAPRO Tab. 10mg	Mochida Pharmaceutical Co., Ltd.	August 22, 2011
Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin) GARDASIL Aqueous Suspension for Intramuscular Injection, GARDASIL Aqueous Suspension for Intramuscular Injection Syringe	MSD K.K.	August 26, 2011
Pancrelipase LipaCreon Granules 300mg Sachet, LipaCreon Capsules 150mg	Abbott Japan Co., Ltd.	August 30, 2011

*1 An additional indication for “treatment of acute rejection after renal transplantation”

*2 An additional dosage and administration for “maximum daily dose, 3 g”

*3 An additional indication for “conduction anesthesia”

*4 An additional indication for “treatment of patients with polyarticular-course juvenile idiopathic arthritis”

*5 An additional indication for “treatment of patients with unresectable pancreatic cancer”

*6 An additional administration for “pediatrics”

*7 An additional indication for “improvement of viraemia in compensated cirrhosis type C in combination therapy with ribavirin”

*8 An additional indication for “suppression of recurrent/relapsed mood episodes in patients with bipolar disorder”

*9 An additional indication for “improvement of viraemia in compensated cirrhosis type C in combination therapy with peginterferon alfa-2a (genetical recombination)”