Pharmaceuticals and Medical Devices Safety Information

No. 263 November 2009

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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. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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No. 263 November 2009

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

[Outline of Information]

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

To Pharmaceuticals and Medical Devices Safety Management Supervisor
—Please use our e-mail alert service—

The Pharmaceuticals and Medical Devices Agency is providing a "Pharmaceuticals and Medical Devices Information E-mail Alert Service" (http://www.info.pmda.go.jp/info/idx-push.html, Japanese only), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of PRECAUTIONS is issued. You are encouraged to register to and use the service.

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 authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

1

Association between use of human insulin and insulin analogues and risk of cancer

1. Introduction

With regard to an increased risk of cancer associated with human insulin and insulin analogues (see Table, to be referred to as "insulin preparations" in the following text), no specific precaution has been included in the package inserts so far. It was concluded at the time of the approval review that, considering their clinical dose, the insulin preparations are unlikely to affect safety in humans, although cell growth activity and development of breast tumors had been noticed in non-clinical studies.

However, a number of study reports on an increased risk of cancer in association with insulin preparations have recently been submitted to Pharmaceuticals and Medical Devices Association (PMDA).[1,2)] On June 26, 2009, four epidemiological studies regarding an increased risk of cancer in association with insulin glargine were published in the Journal of the European Association for the Study of Diabetes (EASD)[3-6)] and, following this, European Medicines Agency (EMEA) and U.S. Food and Drug Administration (FDA) announced on June 29, 2009 and July 1, 2009, respectively, that patients with diabetes taking insulin glargine are adviced to continue their treatment and they should consult their doctor, while EMEA and FDA began to review the association insulin glargine and the risk of cancer.[7,8)]

In Japan, the Japan Diabetes Society announced on July 1, 2009, that patients being treated with insulin glargine are recommended to continue their treatment and consult their doctor,[9)] and PMDA posted its announcement on PMDA InfoWeb on July 13, 2009.[10)]

On the basis of the above, PMDA has conducted a review of insulin preparations, including insulin glargine, with respect to their association with increased risk of cancer and assessed whether safety measures are necessary. The results of the review are summarized in this section.

2. Literature on increased risk of cancer

A review of the literature on the association between use of insulin preparations and increased risk of cancer was performed in the categories of 1) epidemiological studies, 2) non-clinical studies, and 3) measures taken by foreign regulatory agencies.

1) Epidemiological studies

As a result of the investigation of available published epidemiological studies regarding an increased risk of cancer in association with insulin preparations, it was found that there are studies that insulin glargine showed both increased risk of cancer [2, 6, 11-20)] and no risk compared with the other insulin preparations [6, 21-25)]. It was mentioned that insufficient adjustment for confounding factors such as family history was present as a limitation in a number of epidemiological studies.

Regarding insulin glargine, in particular, it was found that there are studies that insulin preparations showed both increased risk of cancer [3-5)] and no risk [3,4)] compared with the other insulin preparations.

2) Non-clinical studies

The non-clinical data submitted at the time of application for approval of insulin analogues demonstrated that cell proliferation induced by insulin analogues is of a similar magnitude to that induced by human insulin, and therefore, at the time of approval review, it was concluded that it was not necessary to include any specific precautions in the package insert.

After approval of insulin analogues, studies on the influence of insulin analogues on cancer cell proliferation have been published,[26,27] in which cell proliferation activity level of insulin analogues was reported to be similar to that of human insulin.

3) Measures taken by foreign regulatory agencies

Package inserts used in foreign countries do not include any information giving precaution of an increased risk of cancer.

FDA announced on July 1, 2009, that it had started reviewing data regarding an increased risk of cancer associated with insulin glargine.[8] EMEA concluded on July 23, 2009, that the currently available data does not suggest a causal relationship between insulin glargine and cancer, and that changes of the current treatment is therefore not necessary. However, the press release stated that EMEA requested the marketing authorization holder (MAH) of insulin glargine to develop a strategy for generation of further research in this area.[28]

3. Results of the review regarding necessity of safety measures

On the basis of the currently available data regarding a possible increased risk of cancer associated with insulin preparations, taking into account of the expert's discussion, PMDA has evaluated the necessity of implementing new safety measures, and has concluded that, at this time, no additional safety measures are needed for insulin preparations including insulin glargine, for reasons (1) and (2) stated below.

(1) Association between use of insulin preparations in general and risk of cancer

1) In the epidemiological studies regarding an increased risk of cancer in association with insulin preparations, it was found that there are studies that insulin glargine showed both increased risk of cancer and no risk compared with the other insulin preparations. Insufficient adjustment for confounding factors such as family history was present as a limitation in most of those studies. Therefore, they cannot be considered to provide sufficient evidence that confirms a causal relationship between insulin preparations and an increased risk of cancer.
2) The non-clinical data submitted at the time of application for approval of insulin analogues demonstrated that cell proliferation induced by insulin analogues is of a similar magnitude to that induced by human insulin. Therefore, it was concluded at the time of approval review, that it was not necessary to include any specific precaution in the package insert. Also, a review of several reports published after the approval did not lead to a change in this conclusion.
3) Package inserts used in foreign countries do not currently include any information giving precaution of an increased risk of cancer.

(2) Association between use of insulin glargine and risk of cancer

1) Regarding insulin glargine, it was found that there are studies that insulin preparations showed both increased risk of cancer and no risk compared with the other insulin preparations in epidemiological studies. Those results were found to be inconsistent
2) Non-clinical studies showed that cell proliferation induced by insulin glargine is of a similar magnitude to that induced by human insulin. Furthermore, when compared with cell proliferation induced by other insulin analogues, insulin glargine was not considered to be associated with an increased risk of cancer.
3) Regarding increased risk of cancer in association with insulin glargine, EMEA does not consider it necessary at the present time to take any action, and package inserts used in foreign countries do not include any information giving precaution of an increased risk of cancer.

4. Future safety measures

At present, given that the association between insulin preparations and cancer has not been suggested, PMDA does not consider it necessary to alert the risk of cancer. However, it will continue to closely watch out for further reports on the matter, and to consider necessary safety measures in the future.

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Table

Nonproprietary name	Brand name	MAH
Human insulin	Novolin R Injection 100 U/mL, etc. Humulin R Injection 100 U/mL, etc.	Novo Nordisk Pharma Ltd. Eli Lilly Japan K.K.
Insulin aspart	NovoRapid Injection 100 U/mL, etc.	Novo Nordisk Pharma Ltd.
Insulin glargine	Lantus Injection 100 U/mL, etc.	sanofi-aventis K.K.
Insulin glulisine	Apidra Injection 100 U/mL, etc.	sanofi-aventis K.K.
Insulin detemir	Levemir Injection Penfill, etc.	Novo Nordisk Pharma Ltd.
Insulin lispro	Humalog Injection 100 U/mL, etc.	Eli Lilly Japan K.K.

2

Important Safety Information

This section presents contents of revisions and a case summary 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 Notification dated September 28, 2009.

1 Ivermectin

Brand name (name of company)	Stromectol Tablets 3 mg (Banyu Pharmaceutical Co., Ltd.)
Therapeutic Category	Anthelmintics
Indications	1. Strongyloidiasis of the intestinal tract 2. Scabies

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder involving significant elevation of AST (GOT), ALT (GPT), etc., or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration 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 denied) in about the last 3 years (April 1, 2006 to August 12, 2009):

- Hepatic function disorders: 4 cases (no fatal cases)

The number of patients treated with Ivermectin for a year estimated by MAH: approximately 191,393 (April 15, 2008 to April 14, 2009)
Marketed in Japan in: December 2002

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Scabies (multi-drug-resistant Pseudomonas aeruginosa infection, cerebral infarction sequela, pneumonia, urinary tract infection)	9 mg for 1 day	**Hepatic function disorder** Approximately 4 months before administration: The patient was admitted to the hospital. He was transferred to a private room because of multi-drug-resistant Pseudomonas aeruginosa infection confirmed by sputum culture. Hematuria and chylous urine were observed. 27 days before administration: The patient started on fluid replacement with lactated Ringer's solution containing 5% glucose 500 mL/day. 6 days before administration: His condition was complicated with pneumonia, and he required sputum aspiration. Laboratory tests revealed that he was positive for MRSA (methicillin-resistant Staphylococcus aureus, 1+) and Pseudomonas aeruginosa (2+). Day 1 of administration:

				The patient was given a single dose of Ivermectin 9mg for the treatment of scabies. At night, pyrexia (39.3°C) and hepatic function disorders developed. At the time of onset, the patient had severe cerebral infarction and was on oral medications, high-calorie infusion, and a urinary catheter had been inserted after the patient underwent tracheostomy cannula insertion and gastrostomy. Day 1 post-administration: The patient showed pyrexia (41.0°C), and his hepatic function rapidly deteriorated further. CRP: 10.4 mg/dL. arterial blood: Candida (1+), catheter urine: enterococci (3+). The patient was given 100 mg acetaminophen suppository and oral *d*-chlorpheniramine maleate 6 mg/day and loxoprofen sodium hydrate 180 mg/day. The patient also received glycyrrhizinate 60 mL/day by drip infusion. Day 3 post-administration: The following microorganisms were detected: MRSA (1+) and Candida (1+) [intravenous hyperalimentation (IVH) catheter]; and MRSA (1+) and Pseudomonas aeruginosa (1+) [sputum (aspired)]. Pyrexia remitted (body temperature: 36.8°C). Day 4 post-administration: CRP: 16.2 mg/dL; body temperature: 39.5°C. Pyrexia developed again. White blood cell count: 3900/mm^3, granulocytes: 83.5%; lymphocytes: 11.1%. Day 7 post-administration: Pyrexia remitted after administration of levofloxacin hydrate. Day 13 post-administration: CRP: 17.7 mg/dL. Infusion with lactated Ringer's solution containing 5% glucose was terminated. Day 22 post-administration: The patient remained on infusion of glycyrrhizinate 40 mL/day until day 26 post-administration. Day 24 post-administration: The patient was negative for scabies. Day 38 post-administration: Hepatic function disorders remitted.
	Concomitant medications: 5% glucose-lactated Ringer's solution, phenytoin, famotidine, tamsulosin hydrochloride, ambroxol hydrochloride, azulene sulfonate sodium/ L-glutamine, butyric acid bacteria formulations, high-calorie infusion solutions containing multiple vitamins, glucose, amino acids, and electrolytes, high-calorie infusion solutions containing trace elements.			

Clinical Laboratory Values

	3 days before administration	Day of administration	Day 2 post-administration	Day 6 post-administration	Day 10 post-administration	Day 23 post-administration	Day 38 post-administration
AST (GOT) (IU/L)	96	848	435	200	44	23	24
ALT (GPT) (IU/L)	81	475	374	207	86	24	18
γ-GTP (IU/L)	254	372	304	571	514	221	127
LDH (IU/L)	—	—	220	198	211	196	196
Al-P (IU/L)	565	853	833	2279	1939	893	—

2 Everolimus, gusperimus hydrochloride, cyclosporine (oral dosage form, injectable dosage form), tacrolimus hydrate (oral dosage form, injectable dosage form), basiliximab (genetical recombination), mycophenolate mofetil, muromonab-CD3

❶ Everolimus, gusperimus hydrochloride, cyclosporine (oral dosage form, injectable dosage form), tacrolimus hydrate (oral dosage form, injectable dosage form), mycophenolate mofetil, muromonab-CD3

Brand name (name of company)	**Everolimus** Certican Tablets 0.25 mg, 0.5 mg, and 0.75 mg (Novartis Pharma K.K.) **Gusperimus hydrochloride** Spanidin for I.V. Infusion 100 mg (Nippon Kayaku Co., Ltd.) **Cyclosporine (oral dosage form, injectable dosage form)** Sandimmune Capsules 25 mg and 50 mg, Sandimmune Oral Solution, Sandimmune Injection, Neoral Capsules 10 mg, 25 mg, and 50 mg, Neoral Oral Solution 10% (Novartis Pharma K. K.) Amadra Capsules 10 mg, 25 mg, and 50 mg (Toyo Capsule Co., Ltd.) Cicporal Capsules 10, 25, and 50 (Nichi-Iko Pharmaceutical Co., Ltd.) Ciclosporin Capsules 25 mg FC and 50 mg FC (Fuji Capsule Co., Ltd.) Ciclosporin Granules 17%, Ciclosporin Capsules 10 mg Mylan, 25 mg Mylan, and 50 mg Mylan (Mylan Seiyaku Ltd.) **Tacrolimus hydrate (oral dosage form, injectable dosage form)** Graceptor Capsules 0.5 mg, 1 mg, and 5 mg, Prograf Granules 0.2 mg and 1 mg, Prograf Capsules 0.5 mg, 1 mg, and 5 mg, Prograf Injection 5 mg (Astellas Pharma Inc.) **Mycophenolate mofetil** CellCept Capsules 250 (Chugai Pharmaceutical Co., Ltd.) **Muromonab-CD3** Orthoclone OKT3 Injection (Janssen Pharmaceutical K. K.)
Therapeutic Category	Miscellaneous metabolism agents Miscellaneous biological preparations
Indications	**Everolimus** Prophylaxis of rejection in heart transplantation. **Gusperimus hydrochloride** Treatment of acute and accelerated rejection after renal transplantation. **Cyclosporine (oral dosage form, injectable dosage form)** (Oral dosage form: Sandimmune, Neoral) 1. Prophylaxis of organ rejection in kidney, liver, heart, lung, and spleen allogeneic transplants. 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation. 3. Behcet's disease (involving ocular complications). 4. Vulgar psoriasis (refractory or affecting more than 30% of the skin surface), pustular psoriasis, erythrodermic psoriasis, arthropathic psoriasis. 5. Aplastic anemia (severe), pure red cell aplasia. 6. Nephrotic syndrome (frequently relapsing or steroid resistant). 7. Systemic myasthenia gravis (in thymectomized patients in whom steroids are not sufficiently effective or inappropriate due to adverse events; for Neoral only). 8. Atopic dermatitis (for which conventional therapy is not sufficiently effective or inappropriate; for Neoral only). (Oral dosage form: Amadra, Cicporal, Ciclosporin FC, Ciclosporin Mylan)

	1. Prophylaxis of organ rejection in kidney and liver allogeneic transplants. 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation. 3. Behcet's disease (involving ocular complications). 4. Vulgar psoriasis (refractory or affecting more than 30% of the skin surface), pustular psoriasis, erythrodermic psoriasis, arthropathic psoriasis. 5. Aplastic anemia (severe), pure red cell aplasia. 6. Nephrotic syndrome (frequently relapsing or steroid-resistant). 7. Systemic myasthenia gravis (in thymectomized patients in whom steroids are not sufficiently effective or inappropriate due to adverse events). (Injectable dosage form) 1. Prophylaxis of organ rejection in kidney, liver, heart, lung, and spleen allogeneic transplants. 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation. **Tacrolimus hydrate (oral dosage form, injectable dosage form)** 1. Prophylaxis of organ rejection in kidney, liver, heart, lung, and spleen allogeneic transplants. 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation. 3. Myasthenia gravis (only for Prograf Granules 0.2 mg and 1 mg, Prograf Capsules 0.5 mg and 1 mg) 4. Rheumatoid arthritis (limited to the cases in which conventional therapy is not sufficiently effective; only for Prograf Capsules 0.5 mg and 1 mg) 5. Lupus nephritis (for which steroids are not sufficiently effective or inappropriate due to adverse reactions; only for Prograf Capsules 0.5 mg and 1 mg) 6. Refractory (steroid-resistant/steroid-dependent) active ulcerative colitis (limited to moderate-to-severe cases; only for Prograf Capsules 0.5 mg, 1 mg, and 5 mg) **Mycophenolate mofetil** ○ Treatment of refractory rejection in kidney transplants (for patients diagnosed with refractory rejection for whom conventional therapy is ineffective or inappropriate due to adverse reactions). ○ Prophylaxis of organ rejection in kidney, heart, liver, lung, and spleen allogeneic transplants. **Muromonab-CD3** Treatment of acute rejection following renal transplants.

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leukoencephalopathy (PML) may occur; patients should be carefully monitored during and after treatment. If the patient shows any adverse conditions including disturbances in consciousness, cognitive disorders, paralysis (hemiplegia, quadriplegia), or language abnormalities, the patient should undergo diagnostic MRI and cerebrospinal fluid testd. Further, administration should be discontinued, and appropriate measures should be taken.

BK viral nephropathy: BK viral nephropathy may possibly occur. In such cases administration dosage should be decreased or discontinued, and appropriate measures should be taken.

❷ Basiliximab (genetical recombination)

Brand name (name of company)	Simulect I. V. Injection 20 mg, Simulect I. V. injection 10 mg for Pediatric (Novartis Pharma K. K.)
Therapeutic Category	Miscellaneous biological preparations
Indications	Prevention of acute rejection in renal transplants

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Progressive multifocal leukoencephalopathy (PML): Progressive multifocal leukoencephalopathy (PML) may possibly occur; patients should be carefully monitored during and after treatment. If the patient shows any adverse conditions including disturbances in consciousness, cognitive disorders, paralysis (hemiplegia, quadriplegia), or language abnormalities, the patient should undergo diagnostic MRI and cerebrospinal fluid test. Further, administration should be discontinued, and appropriate measures should be taken.

BK viral nephropathy: BK viral nephropathy may occur. In such cases administration 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 denied) in about the last 3 years (April 1, 2006 to August 24, 2009):

- Progressive multifocal leukoencephalopathy (PML) : 6 cases (3 fatal cases)
- BK viral nephropathy: 57 cases (no fatal cases)

The number of patients treated with Basiliximab for a year estimated by MAH: approximately 81,000 (for FY 2008)

Marketed in Japan in:

February 1986: cyclosporine (oral and injectable dosage forms)
June 1991: muromonab-CD3
June 1993: tacrolimus hydrate (oral and injectable dosage forms)
April 1994: gusperimus hydrochloride
November 1999: mycophenolate mofetil
April 2002: basiliximab (genetical recombination)
March 2007: everolimus

Case Summary
<Tacrolimus hydrate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 30s	Kidney transplantation (chronic hepatitis C, hypertension, hypercholesterolemia, bronchial asthma, bronchiectasis, chronic gastritis, chronic diarrhoea)	0.3 mg or higher for 2894 days ↓ (administration suspended for 4 days) ↓ Unknown dosage for 7 days	**Progressive multifocal leukoencephalopathy (PML) [caused by JC virus]** Approximately 20 years before administration: The patient had chronic renal failure (rapidly progressive glomerulonephritis). Day 1 of administration: The patient underwent living-donor kidney transplant at a different hospital and started on this drug, methylprednisolone, and mycophenolate mofetil. Day 78 of administration: 1.5 mg of this drug was administered. Day 633 of administration: 0.6 mg of this drug was administered. The trough concentration was 1-3 ng/mL. Day 2195 of administration: The dosage was changed to 0.5 mg. The trough concentration was below detection limit (< 1.5 ng/mL).

				Day 2773 of administration: The patient had kidney transplant biopsy. Steroid pulse therapy was started (methylprednisolone was given at 250 mg for one day and at 125 mg for two days.) Day 2878 of administration: The patient complained of difficulty in breathing and anorexia. Day 2887 of administration: Mycophenolate mofetil was replaced by mizoribine. Day 2888 of administration: The patient was hospitalized due to difficulty in breathing and anorexia. Day 2893 of administration: The patient had no memory of the day's events. He complained of headache and pain in both shoulders. Day 2894 of administration (day of discontinuation): The patient had a panic condition, crying out due to severe headache. Administration of this drug was discontinued. 1 day after discontinuation: Brain MRI indicated a demyelinating lesion in the left frontal lobe. The patient suffered headache and systemic pain. 2 days after discontinuation: Cyclosporine 50 mg was started. 3 days after discontinuation: Steroid pulse therapy was started (methylprednisolone 250 mg). 4 days after discontinuation: Spinal fluid PCR revealed the presence of JC virus. 5 days after discontinuation (day of resuming this drug administration): Cyclosporine was replaced by this drug. Day 7 of resumed administration (day of discontinuation of re-administration): Administration of this drug was terminated. 46 days after discontinuation of re-administration: MRI indicated worsening cerebral conditions. The patient was confirmed to be HIV-negative. 51 days after discontinuation of re-administration: EEG showed decreased frontal lobe functions and slow waves (slow α to θ waves). No spikes were observed. 52 days after discontinuation of re-administration: The patient became markedly disoriented. 55 days after discontinuation of re-administration: The patient started on oxygen inhalation. 56 days after discontinuation of re-administration: Upper limb tremor worsened. 66 days after discontinuation of re-administration: The patient died (cause: central respiratory failure). No postmortem examination was performed.
	Concomitant medications: carvedilol, amlodipine besylate, telmisartan, azulene sulfonate sodium/ L-glutamine, bifidobacterial formulation, fluvastatin sodium, hange-shashinto, montelukast sodium, ambroxol hydrochloride, carbocisteine, salmeterol xinafoate, fluticasone propionate, methylprednisolone, mycophenolate mofetil, mizoribine			

<Cyclosporine>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female	Systemic lupus erythematosus	150 mg for 14 months	**Progressive multifocal leukoencephalopathy (PML)** Approximately 4 years and 9 months before administration:

	20s	(unknown)		The patient experienced onset of systemic lupus erythematosus and prednisolone treatment was initiated. Approximately 2 years and 7 months before administration: Cyclophosphamide pulse therapy was started. Day 1 of administration: The patient started taking 150 mg oral dose of cyclosporine, her medical condition was stable. Month 13 of administration: The patient experienced a staggering gait with gradual occurrence of sensory disturbance and hyposthenia on the left side of her body. Month 14 of administration (day of discontinuation): Administration of cyclosporine was discontinued. 3 months after discontinuation: The patient was hospitalized. She was diagnosed with PML; head MRI identified lesions in the cerebellum and pons, particularly in the superior cerebellar peduncle, and JC virus was found in spinal fluid specimens. The patient received symptomatic therapy (details unknown). 6 months after discontinuation: The lesion expanded into the entire pons and spread further into the cerebellum. 7 months after discontinuation: The patient died.
	Concomitant medications: prednisolone, cyclophosphamide			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 50s	Kidney transplant (diabetes mellitus, renal failure)	Dosage unknown for 171 days	**BK viral nephropathy** Medical history: mitochondrial encephalomyopathy and subsequent chronic renal failure. Diabetes mellitus was detected upon preoperative examination. Approximately 11months before administration: The patient started on hemodialysis due to renal failure resulting from chronic glomerulonephritis. 1 day before administration: The patient began taking mycophenolate mofetil. Day 1 of administration: Administration of this drug was commenced. Day 2 of administration: Treatment with methylprednisolone started. Day 3 of administration: ABO-incompatible living donor kidney transplantation was performed using his wife's organ. Basiliximab (genetical recombination) was administered. Day 7 of administration: Basiliximab (genetical recombination) was administered. Day 51 of administration: The patient was discharged from hospital with serum creatinine of 1.1 mg/dL. Day 73 of administration: Serum creatinine level was elevated to 2.4 mg/dL, which was lowered to 1.1 mg/dL by steroid pulse therapy conducted following diagnosis of acute organ rejection. Day 141 of administration: Serum creatinine increased to 1.9 mg/dL. The patient was diagnosed with BK viral nephropathy, because urine cytology

				identified decoy cells and BK virus was found by PCR analysis of urine and blood samples. The dose of this drug and mycophenolate mofetil was reduced, and the patient was given human immunoglobulin. Serum creatinine level was temporarily elevated to 3.2 mg/dL and then decreased to 2.0 mg/dL. Decoy cells disappeared. Day 171 of administration (day of discontinuation): Serum creatinine was increased to 2.4 mg/dL. The presence of decoy cells was again observed. Mycophenolate mofetil was changed to mizoribine. Although decoy cells were no longer observed, renal function further deteriorated with high urine protein excretion (3+). The patient was considered to have presented with organ rejection. The patient received gusperimus hydrochloride. Cyclosporine was replaced by tacrolimus hydrate. Date unknown: Serum creatinine level improved to 1.9 mg/dL.
	Concomitant medications: basiliximab (genetical recombination), mycophenolate mofetil, methylprednisolone			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 30s	Kidney transplant (chronic kidney disease)	Unknown	**BK viral nephropathy** Approximately 17 years before administration: The patient started on hemodialysis with end-stage renal disorder (ESRD) caused by Henoch-Schonlein purpura. Day 1 of administration: The patient began to receive oral cyclosporine and mycophenolate mofetil. Day 5 of administration: Living donor kidney transplantation was performed using an organ from the patient's ABO-compatible and HLA6/6-mismatched mother. Basiliximab (genetical recombination) was administered. The patient started taking oral methylprednisolone. Day 9 of administration: Basiliximab (genetical recombination) was administered. Day 24 of administration: The patient was discharged from hospital. Day 31 of administration: The presence of decoy cells was suggested by urinary sediment examination and confirmed by urine cytology. Despite no deterioration in the function of the transplanted kidney, mild leukocyturia and proteinuria were observed. PCR analysis of blood and urine samples produced positive results for BK virus DNA. Dosage of this drug was reduced based on the possibility that the patient had BK viral nephropathy. Mycophenolate mofetil was discontinued. Day 45 of administration: The patient underwent kidney transplant biopsy, and one sample was collected. The biopsy result was negative for virus infection and staining for SV-40. No apparent deterioration of renal function was observed; leukocyturia and proteinuria both improved.
	Concomitant medications: basiliximab (genetical recombination), mycophenolate mofetil, methylprednisolone			

3 Ciprofloxacin, ciprofloxacin hydrochloride

Brand name (name of company)	**Ciprofloxacin** Ciproxan-I. V. 200 mg and 300 mg (Bayer Yakuhin, Ltd.) Ciprofloxacin Intravenous Drip Infusion 200 mg DK and 300 mg DK (Daiko Pharmaceutical Co., Ltd.) Ciprofloxacin Intravenous Drip Infusion 200 mg NP and 300 mg NP, Ciprofloxacin DU Intravenous Drip Infusion 300 mg/250 mL NP (Nipro Pharma Corporation) Ciprofloxacin Intravenous Drip Infusion 200 mg Chemiphar, Ciprofloxacin Intravenous Drip Infusion 300 mg Chemiphar (Shiono Chemical Co., Ltd.) Ciprofloxacin Intravenous Drip Infusion 200 mg Sawai and 300 mg Sawai, Ciprofloxacin DU Intravenous Drip Infusion 300 mg/250 mL Sawai (Sawai Pharmaceutical Co., Ltd.) Ciprofloxacin Intravenous Drip Infusion 200 mg Taiyo and 300 mg Taiyo (Taiyo Yakuhin Co., Ltd.) Ciprofloxacin Intravenous Drip Infusion 200 mg Nichi-Iko and 300 mg Nichi-Iko, Ciprofloxacin DU Intravenous Drip Infusion 300 mg/250 mL Nichi-Iko (Nichi-Iko Pharmaceutical Co., Ltd.) Ciprofloxacin Intravenous Drip Infusion 200 mg/100 mL Meiji and 300 mg/150 mL Meiji, Ciprofloxacin DU Intravenous Drip Infusion 300 mg/250 mL Meiji (Meiji Seika Kaisha, Ltd.) **Ciprofloxacin hydrochloride** Ciproxan Tablets 100 mg and 200 mg (Bayer Yakuhin, Ltd.) Displotin Tablets 100 mg and 200 mg (Taiyo Yakuhin Co., Ltd.) Sivastan Tablets 200 mg (Tsuruhara Pharmaceutical Co., Ltd.) Shipkisanon Tablets 200 (Towa Pharmaceutical Co., Ltd.) Cifroquinon Tablets 100 and 200 (Nichi-Iko Pharmaceutical Co., Ltd.) Ciflosacin Tablets 200, Ciprofloxacin Tablets 200 mg Tanabe (Choseido Pharmaceutical Co., Ltd.) Primol Tablets 100 mg and 200 mg (Tatsumi Kagaku Co., Ltd.) Flokisyl Tablets 200 (Sawai Pharmaceutical Co., Ltd.) Peiton Tablets 200 (J-Dolph Pharmaceutical Co., Ltd.) Benzing Tablets 200 mg (Yoshindo Inc.)
Therapeutic Category	Synthetic antibacterials
Indications	**Ciprofloxacin** <Applicable microorganisms> Susceptible strains of Staphylococcus, Enterococcus, anthrax, Escherichia coli, Klebsiella, Enterobacter, Pseudomonas aeruginosa, and Legionella species <Applicable conditions> Sepsis, infections secondary to trauma, thermal burn, surgical wound, etc., pneumonia, peritonitis, cholecystitis, cholangitis, and anthrax **Ciprofloxacin hydrochloride** <Applicable microorganisms> Strains of Staphylococcus, Streptococcus, Pneumococcus, Enterococcus, Neisseria gonorrhoeae, anthrax, Escherichia coli, Shigella, Citrobacter, Klebsiella, Enterobacter, Serratia, Proteus, Morganella morganii, Providencia, Haemophilus influenza, Pseudomonas aeruginosa, Acinetobacter, Legionella, and peptostreptococcus species those are susceptible to ciprofloxacin. <Applicable conditions> Superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma, infections secondary to trauma, thermal burn, surgical wound, etc., mastitis, perianal abscess, pharyngitis/laryngitis, tonsillitis, acute bronchitis, pneumonia, infections secondary to chronic respiratory disease, cystitis, pyelonephritis, prostatitis (acute/chronic), epididymitis, urethritis, cholecystitis, cholangitis, infectious enteritis, bartholinitis, intrauterine infections, adnexa uteri infections,

	dacryocystitis, hordeolum, meibomianitis, otitis media, sinusitis, and anthrax

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Fulminant hepatitis, hepatic function disorder, jaundice: Fulminant hepatitis, hepatic function disorder involving a marked increase in AST (GOT), ALT (GPT), etc. or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration 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 denied) in about the last 3 years (April 1, 2006 to July 13, 2009):

- Fulminant hepatitis: 1 case (fatal case)

The number of patients treated with Ciprofloxacin/Ciprofloxacin hydrochloride for a year estimated by MAH: approximately 598,000 (September 2008 to August 2009)

Marketed in Japan in: November 2000: ciprofloxacin
July 1988: ciprofloxacin hydrochloride

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 10s	Pyrexia, malaise (none)	600 mg for 9 days	**Fulminant hepatitis** 6 days before administration: The patient visited a nearby clinic with pyrexia and malaise and was given prescriptions of mefenamic acid, tranexamic acid, rebamipide, betamethasone and *d*-chlorpheniramine maleate, and clarithromycin. Day 1 of administration: The patient revisited the clinic with pyrexia and underwent drip infusion of the present drug and sulbactam sodium-cefoperazone sodium. Day 9 of administration (day of discontinuation): Administration of the present drug was discontinued. 2 days after discontinuation: Hematology tests indicated hepatic function disorder. 6 days after discontinuation: The patient was referred to university hospital and was given ursodeoxycholic acid for the treatment of possibly drug-induced hepatic disorder. 16 days after discontinuation: Malaise was aggravated. 22 days after discontinuation: The patient was urgently admitted to hospital because of worsening liver function test results. 26 days after discontinuation: Steroid pulse therapy was administered. 27 days after discontinuation: The patient was diagnosed with subacute fulminant hepatitis due to the occurrence of grade-2 encephalopathy. Plasmapheresis, hemodialysis, and hemodiafiltration were started. 29 days after discontinuation: The patient was transferred to another hospital for living donor liver transplantation. The patient presented with grade-3 encephalopathy and a yellowish tinge to the eyes. She showed

				no flapping tremor and was negative for hepatitis viral markers. Estimated abdominal CT liver volume was 1082 mL. A small amount of ascites was observed. Head CT identified no abnormalities. The patient received daily plasmapheresis and continuous hemodiafiltration (CHDF) under sedation. She received lactulose and kanamycin monosulfate via a feeding tube. 30 days after discontinuation: The patient was put on ventilator for controlled ventilation due to decreased SpO_2. 31 days after discontinuation: Hepatic function had not improved; liver volume showed a decreasing trend by abdominal CT. Head CT demonstrated a clear presence of edema. 32 days after discontinuation: No improvement was seen for encephalopathy. Living liver transplantation was performed since prothrombin time decreased to less than 50%. Despite postoperative improvement in liver function, the patient did not recover consciousness. Head CT showed findings of cerebral edema. Administration of glycerol and D-mannitol was started; CHDF was performed. The patient's cerebral edema worsened thereafter. 53 days after discontinuation: The patient died of cerebral edema. DLST (test date unknown): Test results were positive for the present drug and mefenamic acid.
	Concomitant medications: mefenamic acid, tranexamic acid, rebamipide, betamethasone- *d*-chlorpheniramine maleate, clarithromycin, sulbactam sodium-cefoperazone sodium			

Clinical Laboratory Values

	6 days before administration	2 days before administration	2 days after discontinuation	8 days after discontinuation	22 days after discontinuation	27 days after discontinuation	30 days after discontinuation
AST (GOT) (IU/L)	28	66	286	78	3018	564	116
ALT (GPT) (IU/L)	24	31	327	141	2838	1043	140
Al-P (IU/L)	242	218	—	2032	1474	937	301
γ-GTP (IU/L)	39	35	502	456	208	95	22
LDH (IU/L)	265	573	983	459	1161	426	241
Total bilirubin (mg/dL)	0.3	—	—	0.7	9.2	16.4	11.2
Direct bilirubin (mg/dL)	—	—	—	0.3	6.2	10.7	6.3
Prothrombin time (%)	—	—	—	—	56	14	32
Albumin (g/dL)	—	—	—	3.4	—	2.6	3.2
Ammonia (μmol/L)	—	—	—	—	—	211	286

4 Sunitinib malate

Brand name (name of company)	Sutent 12.5 mg Capsules (Pfizer Japan Inc.)
Therapeutic Category	Miscellaneous antineoplastics
Indications	Imatinib-resistant gastrointestinal stromal tumors Renal cell carcinoma that is metastatic or not suitable for radical surgery

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Disseminated intravascular coagulation (DIC): Disseminated intravascular coagulation (DIC) may occur. Patients should be monitored . If any hematologic abnormalities are observed such as platelet count, serum FDP level, plasma fibrinogen concentration, appropriate measures should be taken including discontinuation of sunitinib administration.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 1 year (June 2008 to August 19, 2009):
- Disseminated intravascular coagulation (DIC): 6 cases (no fatal case)

The number of patients treated with Sunitinib malate for a year estimated by MAH: approximately 1,570 (September 1, 2008 to August 31, 2009)
Marketed in Japan in: June 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Gastrointestinal stromal tumor (metastasis to liver, peritoneum, esophagus, and kidney; renal function disorder)	50 mg for 6 days	**Disseminated intravascular coagulation** 5 years before administration: The patient was diagnosed with a gastrointestinal stromal tumor. [History of prior treatment] Surgery: gastrectomy, hepatectomy, resection of the esophago-jejunal anastomosis, left nephrectomy Medications: imatinib mesilate (final dose: 300 mg) 1 day before administration: PS: 0 Day 1 of administration: Administration of of sunitinib malate was started at 50 mg for treatment of imatinib-resistant gastrointestinal stromal tumor. Day 7 of administration (day of discontinuation): The patient was admitted to hospital due to the occurrence of thrombocytopenia and pulmonary hemorrhage secondary to DIC. Administration of sunitinib malate was discontinued; gabexate mesilate was started at 2000 mg in place. Ten units of human red cell concentrates and 20 units of human platelet concentrates were transfused. 2 days after discontinuation: The patient continued to have minor hemoptysis; 8 units of human red cell concentrates were given. 4 days after discontinuation: The patient suddenly rose from the bed and collapsed onto the floor. He developed respiratory arrest and was placed on artificial ventilation with tracheal intubation. The patient developed pyrexia (around 38.0°C) and low blood pressure (70–80 mmHg); dopamine hydrochloride was administered. The patient's body temperature remained at approximately 38°C

				thereafter. 6 days after discontinuation: Sputum culture identified MRSA (MRSA pneumonia). 10 days after discontinuation: Arbekacin sulfate (200 mg/day) was started for treatment of MRSA pneumonia. 20 days after discontinuation: His breathing stabilized, and the patient was weaned from the ventilator. PS: 4. 21 days after discontinuation: Thrombocytopenia caused by DIC resolved; pulmonary hemorrhage and MRSA pneumonia remitted.
	Concomitant medications: furosemide, brotizolam, daikenchuto, clotiazepam, etizolam, mosapride citrate hydrate			

Clinical Laboratory Values

	5 days before administration	Day 5 of administration	Day 7 of administration (day of discontinuation)		1 day after discontinuation	2 days after discontinuation	4 days after discontinuation	6 days after discontinuation	7 days after discontinuation	12 days after discontinuation	21 days after discontinuation
			At hospital administration	After blood transfusion							
Body temperature (°C)	—	—	—	—	—	—	38.0 to 38.9	—	—	—	—
Hemoglobin (g/dL)	9.6	9.7	6.9	6.3	8.9	5.3	8.5	10.9	10.2	10.5	11.0
WBC (/mm^3)	3400	4700	5500	3700	3800	4000	3800	5300	2300	8800	8500
Neutrophils (segmented) (%)	50	59	—	—	79	84	90	79	75	90	91
PTL ($\times 10^4$/mm^3)	20	10.9	2.3	9.5	3.2	5.6	5.1	8.2	9.5	8.5	38.2
Prothrombin time (%)	100	91	46	48	55	65	66	74	68	61	66
INR	1.00	1.06	1.77	1.71	1.52	1.34	1.33	1.23	1.30	1.43	1.35
APTT (sec)	29.8	34.7	35.4	43.0	45.9	39.7	36.4	36.1	42.7	66.8	40.4
Thrombotest (%)	100<	100<	—	100<	100<	100<	100<	100<	85	78	60
Antithrombin III (%)	—	—	—	61	—	—	80	70	81	74	79
Hepaplastin test (%)	155	130	—	61	70	60	82	68	72	77	58
FDP (μg/mL)	14.2	214.2	—	388.7	595.9	377.0	414.4	197.8	22.9	24.1	18.4
Fibrinogen (mg/dL)	297	195	56	78	84	103	135	283	450	504	401
D-dimer (μg/mL)	8.1	129.1	—	299.0	506.7	297.5	355.1	170.8	19.4	19.2	12.7
PIC (μg/mL)*	—	—	—	—	—	—	—	—	1.2	1.7	—
TAT (ng/mL)*	—	—	—	—	—	—	—	—	75.7	16.0	—
AST (GOT) (IU/L)	33	37	38	30	30	24	27	32	49	37	23
ALT (GPT) (IU/L)	2	11	6	7	7	7	9	11	25	13	18
Total bilirubin (mg/dL)	0.6	0.7	3.6	3.0	3.3	1.5	1.9	1.7	1.9	3.7	2.6
BUN (mg/dL)	17.8	14.3	21.4	18.6	20.1	15.9	14.1	16.6	25.4	25.2	15.1
Creatinine (mg/dL)	1.24	1.02	1.13	1.03	1.02	0.87	0.96	1.01	1.03	0.83	0.91
CRP (mg/dL)	0.3>	0.4	1.8	1.7	2.2	1.5	2.1	8.6	17.3	13.9	7.4

* PIC: plasmin-α_2-plasmin inhibitor complex; TAT: thrombin-antithrombin III complex

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Stage IV renal cell carcinoma (metastasis to lung and bone)	50 mg for 17 days	**Disseminated intravascular coagulation** 1 month before administration: Patient was diagnosed with renal cell carcinoma. [History of prior treatment] Surgery: total extirpation of the left kidney Medication: none 2 days before administration: PS: 0 Day 1 of administration: Administration of sunitinib malate was started at 50mg for treatment of renal cell carcinoma (stage IV). The patient developed epistaxis. Day 14 of administration: Thrombocytopenia was observed. Day 17 of administration (day of discontinuation): Anorexia and systemic malaise worsened; the patient became incapable of oral ingestion. She was admitted to hospital with uncontrollable pain related to bone metastasis. Administration of sunitinib malate was discontinued because of decreased hemoglobin, leukopenia, mouth hemorrhage, and nausea. Since the platelet count had decreased to $1.2\times10^4/mm^3$, 10 units of human platelet concentrates and 2 units of human red cell concentrates were transfused. 3 days after discontinuation: Platelet count further decreased to $0.8\times10^4/mm^3$ despite a blood transfusion. The patient showed moderate marrow depression, with a white blood cell count of $3200/mm^3$ and hemoglobin concentration of 7.2 g/dL. The patient's general condition deteriorated and progressed to DIC. Multi-organ failure occurred secondary to DIC. Blood pressure decreased to 80–90 mmHg. Circulatory failure was also observed. The patient was given 2 units of fresh-frozen plasma, dopamine hydrochloride, gabexate mesilate, dried human antithrombin III concentrates, cefozopran hydrochloride (for infection prevention), etc. 4 days after discontinuation: Leukopenia resolved. 12 days after discontinuation: Thrombocytopenia and DIC resolved. 14 days after discontinuation: Epistaxis and mouth hemorrhage resolved. 18 days after discontinuation: PS: 4.
	Concomitant medications: loxoprofen sodium hydrate, rebamipide, urea, magnesium oxide, daikenchuto, zoledronate hydrate, oxycodone hydrochloride hydrate, prochlorperazine maleate, brotizolam, furosemide			

Clinical Laboratory Values

	3 days before administration	Day 14 of administration	Day 17 of administration (day of discontinuation)	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation	10 days after discontinuation	19 days after discontinuation
Body temperature (°C)	—	—	—	36.8	—	—	37.8	—
Hemoglobin (g/dL)	9.2	12.1	—	7.2	—	—	7.6	8.1
WBC (/mm^3)	10310	8560	—	3200	—	—	4270	6130
Neutrophils (segmented) (%)	77.4	93.2	—	77.2	—	—	75.7	65.3
PTL (×10^4/mm^3)	44.5	7.1	1.2	0.8	—	—	5.3	38.3
Prothrombin time (%)	99	—	—	—	—	—	132	—
INR	1.04	—	—	—	0.98	0.96	0.88	—
APTT (sec)	32.4	—	—	—	—	—	36.3	—
Antithrombin III (%)	—	—	—	69	—	—	99	—
FDP (μg/mL)	—	—	—	15.0	40.8	66.4	20.4	—
Fibrinogen (mg/dL)	—	—	—	168	161	170	262	—
D-dimer (μg/mL)	—	—	—	8.50	—	—	—	—
AST (GOT) (IU/L)	16	33	—	79	—	—	41	28
ALT (GPT) (IU/L)	19	25	—	43	—	—	42	39
Total bilirubin (mg/dL)	0.4	0.7	—	2.7	—	—	0.9	0.7
BUN (mg/dL)	18	13	—	44	—	—	39	34
Creatinine (mg/dL)	1.00	1.35	—	3.68	—	—	1.24	1.01
CRP (mg/dL)	4.025	6.317	—	21.211	—	—	1.812	1.303

5 Sorafenib tosilate

Brand name (name of company)	Nexavar 200 mg Tablets (Bayer Yakuhin Ltd.)
Therapeutic Category	Miscellaneous antineoplastics
Indications	Radically unresectable or metastatic renal cell carcinoma, unresectable hepatocellular carcinoma

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Renal failure: Renal failure may occur; patients should be closely monitored. If any abnormalities are observed, administration 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 denied) in about the last 1 year (April 2008 to August 3, 2009):

- Renal failure: 5 cases (no fatal case)

The number of patients treated with Sorafenib tosilate for a year estimated by MAH: approximately 3,000 (September 2008 to August 2009)
Marketed in Japan in: April 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Renal cell carcinoma (metastasis to lung and lymph node, renal failure)	800 mg for 16 days	**Renal impairment** Day 1 of administration: Administration of sorafenib tosilate was started at 800 mg. Day 14 of administration: Rash occurred. Day 16 of administration (day of discontinuation): Creatinine level increased to 7.5 mg/dL. The patient was found to have renal impairment. Administration of this drug was discontinued. 9 days after discontinuation: Rash remitted. 11 days after discontinuation: Renal impairment remitted.
	Concomitant medications: none			

Clinical Laboratory Values

	1 day before administration	Day 6 of administration	Day 12 of administration	Day 16 of administration (day of discontinuation)	3 days after discontinuation	9 days after discontinuation	11 days after discontinuation
Creatinine (mg/dL)	1.7	1.7	1.7	7.5	5.8	2.3	1.7
BUN (mg/dL)	25	25	24	59	58	30	21
Na (mEq/L)	142	139	141	136	136	142	143
K (mEq/L)	4.6	4.8	5.1	4.9	5.0	3.8	3.6
Cl (mEq/L)	108	105	108	105	108	101	105

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Renal cell carcinoma (metastasis to lymph node, hypertension)	800 mg for 35 days	**Renal impairment** Day 1 of administration: Administration of sorafenib tosilate was started at 800 mg. Day 6 of administration: Hypertension was observed. Day 9 of administration: Administration of candesartan cilexetil was started at 8 mg for treatment of hypertension. Day 11 of administration: Hand and foot skin reaction (grade 1) was noted. Day 12 of administration: Treatment with diphenhydramine ointment and mometasone furoate cream was started for the hand and foot skin reaction. Day 15 of administration: The patient was started on ebastine OD at 5 mg for treatment of the hand and foot skin reaction. Day 28 of administration: The hand and foot skin reaction resolved, but hypertension failed to improve. Day 33 of administration: Vomiting occurred. Day 35 of administration (day of discontinuation):

				Renal impairment occurred. The patient was urgently transferred to hospital. Administration of sorafenib tosilate was discontinued. 17 days after discontinuation: Vomiting resolved without particular treatment. Renal impairment also resolved.
	Concomitant medications: diphenhydramine, mometasone furoate, ebastine, candesartan cilexetil			

Clinical Laboratory Values

	Day 1 of administration	Day 6 of administration	Day 12 of administration	Day 28 of administration	Day 35 of administration (day of discontinuation)	2 days after discontinuation	10 days after discontinuation	153 days after discontinuation
Creatinine (mg/dL)	1.1	1.1	1.4	2.0	5.5	5.5	1.4	1.0
BUN (mg/dL)	13.4	—	—	—	59.1	—	—	21.8
Na (mEq/L)	137	—	—	—	129	—	—	135
K (mEq/L)	4.8	—	—	—	6.5	—	—	5.0
CRP (mg/dL)	8.1	—	9.1	4.2	—	—	—	—

6 Tegafur/Gimeracil/Oteracil potassium

Brand name (name of company)	TS-1 Combination Capsules T20 and T25, TS-1 Combination Granule T20 and T25 (Taiho Pharmaceutical Co., Ltd.)
Therapeutic Category	Antimetabolites
Indications	Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary cancer

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Heart failure: Heart failure may occur. Patients should be closely monitored. If any abnormalities are observed, administration 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 denied) in about the last 3 years (April 1, 2006 to July 31, 2009):

- Heart failure: 4 cases (no fatal cases)

The number of patients treated with Tegafur/Gimeracil/Oteracil potassium for a year estimated by MAH: approximately 150,000 (January to December 2008)
Marketed in Japan in: March 1999

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Scirrhous gastric cancer (hypertension)	100 mg for 296 days (3-week treatment followed by 1-week rest period)	**Heart failure** Day 1 of administration: Treatment of scirrhous gastric cancer (peritoneal dissemination following total gastrectomy) was started using the present drug. Day 178 of administration: The patient complained for the first time of staggering gait. Orthostatic dizziness was noted. Blood pressure had fallen to 96/56 mmHg with a pulse rate of 56/min.

				Day 192 of administration: The patient reported experiencing staggering gait. Blood pressure was 100/58 mmHg with a regular pulse rate of 62/min. He also reported having occasional diarrhoea. Day 206 of administration: The patient mentioned having staggering gait and orthostatic dizziness. The blood pressure measurement at the clinic was 126/60 mmHg, although the patient said the home blood pressure was constantly below 100 mmHg. Day 238 of administration: Hypotension persisted despite discontinuation of olmesartan medoxomil therapy. The patient's general condition showed no improvement. Day 273 of administration: Hypotension still persisted in spite of termination of nifedipine treatment. General condition showed no improvement. Day 283 of administration: Chest x-ray film revealed left lung congestion, left interlobar plural effusion, and cardiothoracic ratio of 51%. BNP was significantly elevated (2901 pg/mL). The patient was diagnosed with cardiac failure. ECG showed left atrial enlargement, negative T wave (in aVL), mild ST depression (in I and V6: 1 mm), QTc prolongation (> 450 msec), and mild ischemic findings. QRS axis was normal, and no left ventricular hypertrophy was noted. Pulse rate was 59/min. Treatment with furosemide (20 mg) and spironolactone (25 mg) was commenced (27 days). The patient had concurrent urinary tract infection and left hydronephrosis. Presence of ascites was noted. Blood pressure was 102/66 mmHg. Day 286 of administration: Atenolol was discontinued. All hypotensives were also discontinued. Heart failure did not improve, and hypotension continued. Day 296 of administration (day of discontinuation): Administration of the present drug was terminated. Subsequently, staggering gait and orthostatic dizziness gradually resolved, and blood pressure increased. 22 days after discontinuation: Blood pressure measurement was 148/78 mmHg. The patient had no orthostatic dizziness and no staggering gait. 84 days after discontinuation: Blood pressure was 162/76 mmHg, with BNP of 250.6 pg/mL. Following discontinuation of the present drug, blood pressure showed a marked increase, and heart failure remitted.
	Concomitant medications: olmesartan medoxomil, nifedipine, atenolol			

Clinical Laboratory Values

	Day 178 of administration	Day 192 of administration	Day 206 of administration	Day 283 of administration	22 days after discontinuation	84 days after discontinuation
BNP (pg/mL)	—	—	—	2901	—	250.6
Systolic blood pressure (mmHg)	96	100	126	102	148	162
Diastolic blood pressure (mmHg)	56	58	60	66	78	76
Pulse rate (/min)	56	62	—	59	—	—
Cardiothoracic ratio (%)	—	—	—	51	—	—

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Large intestine carcinoma (not reported)	80 mg for 89 days (including rest period)	**Heart failure** Day 1 of administration: Administration of the present drug was started for treatment of large intestine carcinoma (with metastasis to lung and liver; high anterior resection of the rectum had been performed). Day 90 of administration (day of discontinuation): The patient developed sudden onset of dyspnea and was transported to the emergency unit. Chest X-ray and CT examination showed pulmonary congestion. She was diagnosed with heart failure. The present drug was discontinued due to disease progression. Oxygen inhalation and furosemide (20 mg) therapy were initiated (until 3 days after discontinuation). 11 days after discontinuation: Whereas heart failure indicated an improving trend, he still required to be hospitalized. 14 days after discontinuation: The patient maintained an improving pattern without any noteworthy adverse changes. The patient was discharged from hospital.
	Concomitant medications: none			

Clinical Laboratory Values

	Day 1 of administration	1 day after discontinuation	2 days after discontinuation	4 days after discontinuation
WBC (/mm^3)	9900	10600	11300	10300
Neutrophils (%)	76.1	82	71.2	76.8
Hemoglobin (g/dL)	11.3	11.8	11.2	11.9
Platelet count ($\times10^4$/mm^3)	33.1	33.5	30.3	24.4
Total bilirubin (mg/dL)	1	0.9	0.9	1.3
AST (GOT) (IU/L)	42	82	75	110
ALT (GPT) (IU/L)	20	29	27	30
LDH (IU/L)	1124	991	904	1408
BUN (mg/dL)	10.2	11	14.7	14.7
Blood creatinine (mg/dL)	0.45	0.4	0.47	0.36

7 Bevacizumab (genetical recombination)

Brand name (name of company)	Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Unresectable colorectal cancer advanced and recurrent

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: Interstitial pneumonia may occur, Patients should be closely monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> This product is approved for only in combination use with fluoropyrimidine-based anti-tumor chemotherapy and oxaliplatin (e.g., FOLFOX therapy).
Interstitial pneumonia in FOLFOX therapy has been also reported at an incidence rate of 0.2% (based onsurvey including use-result survey of oxaliplatin).
When this product was used in combination with FOLFOX therapy, interstitial pneumonia occurred at an incidence rate of 0.12% (38 cases/ 31,377 estimated number of treated patientssince marketed). In 21 cases (no fatal cases), the causality to the drug could not be denied.
Marketed in Japan: June 2007

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Metastatic colon cancer (hepatitis C)	5 mg/kg for 1 day	**Interstitial pneumonia** Approximately 11 months before administration: The patient was diagnosed with primary colon cancer. 288 days before administration: Chest CT findings: bilateral emphysema and reticular shadow in bilatereal lungs (bilateral old inflammatory changes). 268 days before administration: The patient underwent sigmoidectomy. 221 days before administration: The patient underwent partial hepatectomy. 204 days before administration: Chest X-ray: reticular shadow in right lower lung 200 days before administration: Administration of mFOLFOX6was initiated for treatment of metastatic colon cancer (to the liver). Day 1 of administration: Administration of this product was initiated at 5 mg/kg in combination with mFOLFOX6.Administration of mFOLFOX6 and this product (5 mg/kg) was discontinued after this first administration. [Physical condition before administration of this product] ○ Signs/symptoms: none 10 days after discontinuation: The patient experienced shortness of breath and pyrexia. The patient developed interstitial pneumonia. 20 days after discontinuation: The patient visited an ambulatory clinic and was diagnosed with interstitial pneumonia. [Physical condition and chest X-ray and CT findings at the initial occurence of interstitial lung disease] ○ Signs/symptoms: dry cough, pyrexia, malaise, dyspnoea, and fatigability ○ Chest X-ray:reticular shadow in left lower lung ○ Chest CT: new reticular shadow in left lower lung 21 days after discontinuation: The patient was hospitalized and oral administration of cefepime hydrochloride hydrate at 4 g (until 26 days after discontinuation) and prednisolone at 50 mg was initiated. 23 days after discontinuation: Symptoms were remitted. 26 days after discontinuation: Symptoms were in remission and the patient left the hospital. 32 days after discontinuation: Chest CT: decrease of reticular shadow in left lower lung

				36 days after discontinuation: Chest X-ray: decrease of reticular shadow in the left lower lung 49 days after discontinuation: Interstitial pneumonia was once in remission and prednisolone dose was reduced. However, the interstitial pneumonia relapsed with concurrent infections. The patient was transferred to another hospital. The patient recovered after treatment with steroid pulse therapy. 56 days after discontinuation: Drug lymphocyte stimulation test (DLST) yielded a positive result only for this product (SI value: 208%), although oxaliplatin, fluorouracil, and levofolinate calcium were tested as well. 80 days after discontinuation: The patient was transferred to thehospital. 82 days after discontinuation: Chest X-ray: no change in reticular shadow Chest CT: no change in reticular shadow 113 days after discontinuation: The patient had sequel of interstitial pneumonia (requiring home oxygen therapy). This product was not readministerd to the patient.
	Concomitant medications: oxaliplatin, fluorouracil, levofolinate calcium			

Clinical Laboratory Values

	Day 1 of administration	20 days after discontinuation	25 days after discontinuation	32 days after discontinuation	81 days after discontinuation	109 days after discontinuation
WBC (/mm^3)	3800	7100	15200	15000	8600	13400
LDH (IU/L)	—	—	—	—	296	325
CRP (mg/dL)	0.3	5.1	0.3	0.1	0.6	0.1
KL-6 (U/mL)	—	721	—	—	534	544
SP-D (ng/mL)	—	473	—	—	205	288
SP-A (ng/mL)	—	116	—	—	—	—

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Metastatic colon cancer (diabetes mellitus and hypertension)	10 mg/kg in every two weeks for 13 courses	**Interstitial pneumonia** Approximately 4 months before administration: The patient was diagnosed with primary colon cancer (stage IV). 101 days before administration: The patient underwent left hemicolectomy. 41 days before administration: Administration of tegafur/uracil was initiated as postoperative adjuvant chemotherapy (until 28 days before administration). 7 days before administration: Chest X-ray: no abnormal findings 6 days before administration: Chest CT: no pulmonary metastasis and no abnormal findings Day 1 of administration: Administration of this product was initiated at 10 mg/kg in combination with mFOLFOX6 for treatment of metastatic colon cancer (in the liver). Day 166 of administration (day of discontinuation):

				Administration of the mFOLFOX6 and this product (10 mg/kg) was discontinued. 14 days after discontinuation: The patient developed interstitial pneumonia. Chest CT: minor ground-glass shadow inright lower lung The patient experienced malaise (grade 1) and anorexia (grade 1), but no dyspnea. 16 days after discontinuation: Systemic malaise worsened, and the patient suffered breathing difficulty and pyrexia. The patient visited an ambulatory clinic and was hospitalized to ICU for suspected diagnosis of interstitial pneumonia by chestX-ray. Drip infusion of antibiotics was initiated. Signs/symptoms: dyspnoea, sputum, pyrexia, malaise Auscultation: velcro rales Chest X-ray: ground-glass shadows in whole right lung field and left upper lung field. 17 days after discontinuation: Interstitial pneumonia was suspected by chest CT.Tthe patient consulted with the respiratory team and was diagnosed with drug-induced interstitial pneumonia. Administration of oxygen (by reservoir mask) was initiated. Chest CT: ground-glass shadows in whole right lung field and left upper lung field Sputum culture: Staphylococcus aureus (non-MRSA) and α-streptococci were detected (with possibly of contamination with oral bacteria). β-D-glucan was negative. 18 days after discontinuation: Administration of prednisolone was initiated at 40 mg. 20 days after discontinuation: Prednisolone dose was increased to 60 mg due to the lack of significant improvement in chest X-ray. The patient was mycoplasma-negative. 26 days after discontinuation: ChestX-ray indicated improvement tendency.Prednisolone dose was reduced to 50 mg. 31 days after discontinuation: Prednisolone dose was reduced to 40 mg. 37 days after discontinuation: Interstitial pneumonia was in remission. Chest X-ray: abnormal shadows in left lung disappeared almost completely. Ground-glass shadow still remains in whole right lung field with improvement tendency.
	Concomitant medications: oxaliplatin, fluorouracil, levofolinate calcium, granisetron hydrochloride, dexamethasone sodium phosphate			

Clinical Laboratory Values

	Day 1 of administration	14 days after discontinuation	17 days after discontinuation	19 days after discontinuation	23 days after discontinuation	34 days after discontinuation
WBC (/mm^3)	4700	4700	3600	7100	10500	11300
LDH (IU/L)	658	421	404	428	604	370
CRP (mg/dL)	1.37	6.83	18.14	5.46	1.41	0.15
KL-6 (U/mL)	—	—	1310	—	—	—
SP-D (ng/mL)	—	—	698	—	—	—

8 Rosuvastatin calcium

Brand name (name of company)	Crestol Tablets 2.5 mg and 5.0 mg (AstraZeneca K. K.)
Therapeutic Category	Hyperlipidemia agents
Indications	Hypercholesterolemia, familial hypercholesterolemia

《**PRECAUTIONS** (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Thrombocytopenia: thrombocytopenia may occur; patients should be closely monitored by conducting blood and other tests. If any abnormalities are observed, administration 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 denied) in about the last 3 years (April 1, 2006 to August 6, 2009)
- Thrombocytopenia: 7 cases (no fatal cases)

The number of patients treated with Rosuvastatin calcium for a year estimated by MAH: approximately 2,055,000 (September 2008 to August 2009)
Marketed in Japan in: April 2005

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Dyslipidemia (congestive cardiac failure)	2.5 mg for 7 days	**Thrombocytopenia** 30 days before administration: Patient was hospitalized with congestive cardiac failure. Administration of heparin sodium was initiated. 12 days before administration: Administration of torasemide was initiated. 11 days before administration: Administration of imidapril hydrochloride was initiated. Day 1 of administration: Dyslipidemia became pronounced with the improvement of congestive cardiac failure following hospitalization. Administration of this drug was initiated. Day 4 of administration: The patient developed thrombocytopenia. blood sample analysis indicated that platelet count was reduced to $9.0\times10^4/mm^3$. Day 7 of administration (day of discontinuation): Platelet count further decreased to $6.0\times10^4/mm^3$ Administration of this drug was discontinued. 6 days after discontinuation: Platelet count was improved to $10\times10^4/mm^3$. The patient left the hospital. 62 days after discontinuation: The patient underwent re-examination at an ambulatory clinic. Platelet count was improved to $18.1\times10^4/mm^3$, indicating recovery from thrombocytopenia.
	Concomitant medications: torasemide, imidapril hydrochloride			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Hypercholesterolemia (none)	2.5 mg for 93 days	**Thrombocytopenia** Day 1 of administration: Administration of this drug was initiated for treatment of hypercholesterolemia. The patient reported no symptoms. Platelet count was $20.1\times10^4/mm^3$. Day 33 of administration: The patient reported no symptoms. Day 64 of administration: The patient reported no symptoms. Around day 89 of administration: The patient felt thirsty. Day 92 of administration: The patient noticed development of localized oral submucosal hemorrhage (blood blister-like). This repeatedly developed at different sites. Day 93 of administration (day of discontinuation): The patient was diagnosed with thrombocytopenia with platelet count of $3.0\times10^4/mm^3$, uric protein (-) and uric blood (2+). This drug was discontinued and the patient's clinical course was observed. 3 days after discontinuation: The patient developed frequent occurrence of localized oral submucosal hemorrhage and felt tongue pain. Hemorrhagic redness was observed over the extremities. The patient was referred to another hospital and hospitalized. Prednisolone was administered at 1 mg/kg and the patient revealed good clinical course. 11 days after discontinuation: The patient left the hospital. Administration of prednisolone was continued. 13 days after discontinuation: The patient revisited the hospital. Hemorrhagic diatheses disappeared.
	Concomitant medications: none			

3

Revision of PRECAUTIONS

(No. 210)

(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 28 and October 19, 2009 (excluding those presented in "2. Important Safety Information" of this Bulletin).

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1 **<Skeletal muscle relaxants>**

Pancuronium Bromide, Vecuronium Bromide, Rocuronium Bromide

[Brand Name] Mioblock Intravenous 4 mg (Shering-Plough K.K.)
Musculax Intravenous 4 mg and 10 mg (Shering-Plough K.K.) and others
Eslax Intravenous 25 mg/2.5mL and 50 mg/5.0 mL (Shering-Plough K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Bronchospasm:** Bronchospasm may occur. Patients should be closely monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

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2 **<Antiarrhythmic agents>**

Amiodarone Hydrochloride (oral dosage form)

[Brand Name] Ancaron Tablets 100 (Sanofi-Aventis K.K.) and others

[Important Precautions] Chest X-ray or chest computed tomography

[Adverse reactions (clinically significant adverse reactions)] **Interstitial pneumonia, pulmonary fibrosis and alveolitis:** Interstitial pneumonia, pulmonary fibrosis, or alveolitis may occur, which can lead to fatal outcome. If chest X-ray or chest computed tomography reveals any abnormal shadows or if symptoms including cough, dyspnea and crepitations are observed, the above adverse drug reactions should be suspected. In such cases, administration should be discontinued and appropriate measures such as steroid therapy should be taken as needed.
Reduction of pulmonary diffusing capacity by 15% and more may predict the development of above adverse drug reactions. In such cases, appropriate0 examinations should be conducted more frequently.

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3 **<Antiarrhythmic agents>**

Amiodarone Hydrochloride (injectable dosage form)

[Brand Name] Ancaron Injection 150 (Sanofi-Aventis K.K.)

[Adverse reactions (clinically significant adverse reactions)] **Interstitial pneumonia:** Pneumonia may occur, which can lead to fatal outcome. If chest X-ray or chest CT reveals any abnormal shadows or if symptoms including cough, dyspnoea and crepitations are observed, the above adverse drug reactions should be suspected. In such cases, administration should be discontinued and appropriate measures including steroid therapy should be taken as needed.

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4 <Diuretics>

Potassium Canrenoate

[Brand Name] Soldactone for Intravenous Use 100 mg and 200 mg (Pfizer Japan Inc.) and others

[Contraindications] Patients with Addison's disease

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5 <Anticoagulants>

Reviparin Sodium

[Brand Name] Clivarine for Dialysis 1000 Units/mL Vial 5 mL (Abbott Japan Co. Ltd), Lowmorin Inj. (Bayer Yakuhin, Ltd.)

[Contraindications] Patients with a history of hypersensitivity to any of the ingredients of this product or heparin, and other low-molecular-weight heparin

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6 <Antidiabetic agents>

Buformin Hydrochloride

[Brand Name] DIBETOS Tablets 50 mg (Nichi-Iko Pharmaceutical Co., Ltd.) and others

[Important Precautions] Lactic acidosis may occur in a patient receiving this product who undergoes an imaging test with an iodine contrast medium. This drug should therefore be temporarily discontinued before such a test is performed (unless an emergency test is needed). Administration of this drug should be suspended for at least 48 hours after the injection of an iodine contract medium. The patient should be carefully monitored when the administration of the product is resumed.

[Interactions (precautions for concomitant use)] Iodine contrast media [Clinical symptoms and measures: Clinical symptoms include general malaise, feelings of fatigue and weakness associated with clouding of consciousness, and gastrointestinal disorders such as nausea, vomiting, and diarrhea. When iodinated contrast examination is conducted, administration of this drug should be temporarily discontinued. If urgent examination is required, the patient should be carefully monitored for increase in blood lactate levels and decrease in blood pH.]

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7 <Acting mainly on gram-positive and gram-negative bacteria>

Doripenem Hydrate

[Brand Name] Finibax 0.25 g IV Solution and Finibax 0.25 IV Solution Kit (Shionogi & Co., Ltd.)

[Adverse reactions (clinically significant adverse reactions)]

Pancytopenia, agranulocytosis, leucopenia and thrombocytopenia: Pancytopenia, agranulocytosis, leucopenia, or thrombocytopenia may occur. Patients should be closely monitored with periodic hematological examination. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Oculomucocutaneous syndrome (Stevens- Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome): Oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be closely monitored and if abnormalities including fever, cough and dyspnoea are observed, chest X-ray and other appropriate examinations should be conducted immediately. If interstitial pneumonia is suspected, administration should be discontinued and appropriate measures including administration of corticosteroids should be taken.

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8 <Vaccines>
Influenza HA Vaccine, Influenza A (H1N1) HA Vaccine

[Brand Name]	Influenza HA Vaccine “HOKKEN”, Influenza HA Vaccine “S HOKKEN”, and Influenza HA Vaccine “S HOKKEN” Syringe (The Kitasato Institute), Influenza HA Vaccine “KAKETSUKEN” TF (Kaketsuken), Influenza HA Vaccine “SEIKEN” and Flu-Syringe “SEIKEN” (Denka Seiken Co., Ltd.), “BIKEN HA”, FLUBIK HA, and FLUBIK HA Syringe (The Research Foundation for Microbial Diseases of Osaka University), Influenza A (H1N1) HA Vaccine “HOKKEN” and Influenza A (H1N1) HA Vaccine “S HOKKEN” Syringe (The Kitasato Institute), Influenza A (H1N1) HA Vaccine “KAKETSUKEN” (Kaketsuken), Influenza A (H1N1) HA Vaccine “SEIKEN” (Denka Seiken Co., Ltd.), and Influenza A (H1N1) HA Vaccine “BIKEN” (The Research Foundation for Microbial Diseases of Osaka University)
[Precautions of dosage and administration]	A person vaccinated with live vaccines or other inactivated vaccines should receive vaccination with this product with an interval of at least 27 days or 6 days, respectively in principal. However, this product may be vaccinated simultaneously with other vaccines if the physician considers it necessary (this product must not be mixed with other vaccines).
[Vaccination in pregnant, parturient and nursing women]	The safety of this product in pregnant women has not been established. Pregnant women or women with a possible pregnancy should receive vaccination with this product only if the potential benefit outweighs the risk. In addition, some small studies have reported that the incidence of congenital anomaly in vaccinated women was not higher than spontaneous incidence.
<Reference>	Birth Defects and Drugs in Pregnancy, 1977

(2) Medical Devices

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of medical devices that have been revised in according to the Notification dated September 24, 2009.

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1 Blood Circuit

[Brand Name]

Carmiline, etc. (Kawasumi Laboratories, Inc.), Gambro Blood Tubing System, etc. (Gambro), JMS Blood Tubing Line for Artificial Kidney Dialysis, etc. (JMS Co., Ltd.), Blood Tubing Line for Continuous Filtration, etc. (JUNKEN MEDICAL, Co., Ltd.), MERA Blood Tubing Line for Hemodialysis (Senko Medical Instrument Mfg. Co., Ltd.), Blood Tubing Line for Slow Continuous Hemofiltration, etc. (Naniwa Rubber Co., Ltd.), Blood Tubing Line, etc. (Nikkiso Co., Ltd.) Sureflow, etc. (Nipro Corporation), Blood Tubing Line for Artificial Kidney Dialysis(Hanaco Medical Co., Ltd.)

[WARNINGS]

WARNINGS

1) When diluted or dissolved anticoagulants such as heparin sodium are continuously administered, a Luer lock syringe or injection line should be used to connect with the blood circuit. [Inadvertent disconnection of a syringe etc. may cause blood leakage or air intrusion.]
2) When transfusion etc. is continuously administered on the arterial or venous circuit, a Luer lock transfusion set etc. should be used for connection unless using an access port that prevents blood leakage etc. in cases of disconnection. [Inadvertent disconnection of a transfusion set etc. may cause blood leakage or air intrusion.]

The "unless" clause of the section 2) should be inserted only when the blood tubing line is equipped with an access port that prevents blood leakage etc.

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2 Implantable Cardiac Pacemaker

[Brand Name]

Victory DR, etc. (St. Jude Medical Japan Co., Ltd.), Kiklos DR, etc. (Nihon Kohden Corporation), Medtronic EnRhythm, etc. (Medtronic Japan Co., Ltd.), Reply DR, etc. (Japan Lifeline Co., Ltd.), Cylos DR, etc. (Biotronik Japan, Co., Ltd.), Dynamis, etc. (Paramedic Co., Ltd.), Fidelity DR, etc. (Fukuda Denshi Co., Ltd.), and Insignia Plus DR, etc. (Boston Scientific Japan K.K.)

[Important Precautions]

Sequential pulsed irradiation of X-ray beam to the body part implanted may cause oversensing, resulting in a temporary suppression of pacing output. Caution should be exercised not to irradiate the site implanted with X-ray beam (See the "Interactions" section).

[Interactions (precautions for concomitant use)]

Name etc. of medical device	Clinical symptoms and measures	Mechanism and risk factors
X-ray diagnostic equipment, fluoroscopic apparatus, X-ray generator, etc.	• Fluoroscopy tests requiring sequential pulsed irradiation of X-ray beam (sequential fluoroscopy within a few seconds, pulsed fluoroscopy, digital angiography, digital subtraction angiography, cine imaging, etc.) may temporarily suppress pacing, resulting in bradyarrhythmia accompanied by dizziness, fainting, etc. • Sequential pulsed irradiation of X-ray beam should not target the body part implanted. • Attempt if displacement of the pacemaker out of the irradiation site by "holding both arms up" etc. of the patient is an option,	When conducting fluoroscopy tests requiring sequential pulsed irradiation of X-ray beam, output of the pacing pulse of implantable cardiac pacemaker may be temporarily suppressed due to oversensing caused by influencing the C-MOS IC inside the body.

	when tests requiring sequential pulsed irradiation of X-ray beam to the site implanted cannot be avoided. If sequential pulsed irradiation of X-ray beam to the body implanted still cannot be avoided, set to fixed-pacing mode and avoid competitive pacing as well as monitoring pulse. Or prepare and use temporary external pacing.	

3 Implantable Defibrillators

[Brand Name]

Epic+ DR etc. (St. Jude Medical Japan Co., Ltd.), Medtronic Virtuoso DR, etc. (Medtronic Japan Co., Ltd.), Ovatio DR, etc. (Japan Lifeline Co., Ltd.), Lumax 340 DR-T, etc. (Biotronik Japan, Co., Ltd.), Confient, etc. (Boston Scientific Japan K.K.)

[Important Precautions]

Sequential pulsed irradiation of X-ray beams to the body part implanted may cause oversensing, resulting in a temporary suppression of intended treatment or in inappropriate treatment of tachycardia. Caution should be exercised not to irradiate the site implanted with X-ray beams (See the "Interactions" section).

[Interactions (precautions for concomitant use)]

Name etc. of medical device	Clinical symptoms and measures	Mechanism and risk factors
X-ray diagnostic equipment, fluoroscopic apparatus, X-ray generator, etc.	• Fluoroscopy tests requiring sequential pulsed irradiation of X-ray beam (sequential fluoroscopy within a few seconds, pulsed fluoroscopy, digital angiography, digital subtraction angiography, cine imaging, etc.) may cause this product to treat tachycardia inappropriately. • Sequential pulsed irradiation of X-ray beam should not target the body part implanted. • Attempt if displacement of the defibrillator out of the irradiation site by "holding both arms up" etc. of the patient is an option, when tests requiring sequential pulsed irradiation of X-ray beam to the site implanted cannot be avoided. If sequential irradiation of X-ray beam to the body implanted still cannot be avoided, set to fixed-pacing mode and avoid competitive pacing, upon turning off the tachycardia detector as well as monitoring pulse. Or prepare and use temporary external defibrillators or pacing.	When conducting fluoroscopy tests requiring sequential pulsed irradiation of X-ray beam, output of the pacing pulse of implantable defibrillator may be temporarily suppressed or inappropriate pulsation treatment may be conducted due to oversensing caused by influencing C-MOS IC inside the body.

4 X-ray Diagnostic Equipment, etc. (X-ray diagnostic equipment, fluoroscopic apparatus, X-ray generator, etc.)

(Note: Combined medical equipment systems such as therapeutic devices equipped with X-ray diagnostic function are included.)

[Brand Name]

Elekta Synergy (Elekta K.K.), OEC 9900 Series, etc. (GE Healthcare Japan Corporation), AXIOM Artis, etc. (Siemens-Asahi Medical Technologies Ltd.), X-ray Television System SONIALVISION safire 17, etc. (Shimadzu Corporation), MODULITH SLX-F2, etc. (Sumire Medical Corporation), Integra, etc. (Direx Japan Co., Ltd.), X-ray Equipment for Surgery SXT-1000A, etc. (Toshiba Medical Manufacturing Co., Ltd.), X-ray Cardiovascular Diagnostic System Infinix Celeve-i INFX-8000V, etc. (Toshiba Medical Systems Corporation), X-ray Bone Densitometer Discovery, etc. (Toyo Medic Co., Ltd.), Dornier Lithotripter SII, etc. (Dornier MedTech Japan Co., Ltd.), On-Board Imager (OBI), etc. (Varian Medical Systems K.K.), Multi-Purpose Imaging System CUREVISTA, etc. (Hitachi Medical Corporation), Angiographic X-ray Diagnostic Equipment Allura Xper CV20, etc. (Philips Electronics Japan, Ltd.), Linear Accelerator System MHI-TM2000 (Mitsubishi Heavy Industries, Ltd.), Particle Beam Treatment System (proton type), etc. (Mitsubishi Electric Corporation), Inverter Mobile X-ray Equipment YRM-1250, etc. (Yoshida Denzai Kogyo Co., Ltd.)

[Important Precautions]

Sequential pulsed irradiation of X-ray beams to the implanted body part of an implantable cardiac pacemaker or implantable defibrillator may cause the device to malfunction. If irradiation of X-ray beams to the site implanted is unavoidable, appropriate measures should be taken in accordance with the sections “Important Precautions”, “Interactions”, etc. of the package insert of the implantable cardiac pacemaker or implantable defibrillator.

[Interactions (precautions for concomitant use)]

Name etc. of medical device	Clinical symptoms and measures	Mechanism and risk factors
Implantable cardiac pacemaker and implantable defibrillator	• Sequential pulsed irradiation of X-ray beam to the implanted body part of an implantable cardiac pacemaker or implantable defibrillator may cause the device to malfunction. • If sequential pulsed irradiation of X-ray beam to the implanted body part is unavoidable, appropriate measures should be taken in accordance with the sections “Important Precautions”, “Interactions”, etc. of the package insert of the implantable cardiac pacemaker or implantable defibrillator.	When conducting flouoroscopy tests requiring sequential pulsed irradiation of X-ray beams (sequential fluoroscopy within a few seconds, pulsed fluoroscopy, digital angiography, digital subtraction angiography, cine imaging, etc.), output of the pacing pulse of implantable cardiac pacemaker or implantable defibrillator may be temporarily suppressed or inappropriate pulsation treatment may be conducted due to oversensing caused by influencing the C-MOS IC inside the body of implantable cardiac pacemaker or implantable defibrillator.

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 collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of November 1, 2009)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Sorafenib Tosilate Nexavar Tablets 200 mg[*1]	Bayer Yakuhin, Ltd.	May 20, 2009
Valganciclovir Hydrochloride VALIXA Tablets 450 mg[*2]	Mitsubishi Tanabe Pharma Corporation	May 20, 2009
Pemetrexed Sodium Hydrate Alimta Injection 500 mg[*3]	Eli Lilly Japan K.K.	May 20, 2009
Freeze-dried Japanese encephalitis vaccine (cell culture derived) Jebik V	The Research Foundation for Microbial diseases of Osaka University	June 2, 2009
Atomoxetine Hydrochloride Strattera capsule 5mg, 10 mg, and 25 mg	Eli Lilly Japan K.K.	June 19, 2009
Fluticasone Furoate Allermist 27.5 μg 56 metered Nasal Spray	GlaxoSmithKline K.K.	June 19, 2009
Lapatinib Tosilate Hydrate Tykerb Tablets 250 mg	GlaxoSmithKline K.K.	June 19, 2009
Telmisartan, Hydrochlorothiazide Micombi Combination Tablets AP and BP	Nippon Boehringer Ingelheim Co., Ltd.	June 23, 2009
Risperidone RISPERDAL Consta Intramuscular Injection 25 mg, 37.5 mg, and 50 mg	Janssen Pharmaceutical K.K.	June 23, 2009
Insulin Glulisine (Genetical Recombination) APIDRA Inj. Cart, Inj. SoloStar, Inj. 100 units/mL	Sanofi-Aventis K.K	June 24, 2009
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion 100[*4]	Mitsubishi Tanabe Pharma Corporation	July 7, 2009
Etanercept (Genetical Recombination) ENBREL 25 mg Syringe for S.C. Injection[*5]	Wyeth K.K.	July 7, 2009
Somatropin (Genetical Recombination) Growject injection 1.33 mg, 8 mg, BC 8 mg[*6]	JCR Pharmaceuticals Co., Ltd.	July 7, 2009
Follitropin alfa (Genetical Recombination) Gonalef 75, Gonalef Pen 450 and 900[*7]	Merck Serono Co., Ltd.	July 7, 2009

Levofloxacin Hydrate CRAVIT TABLETS 250 mg, 500 mg, Fine Granules 10%	Daiichi Sankyo Company, Limited.	July 7, 2009
Clozapine CLOZARIL Tablets 25 mg, 100 mg	Novartis Pharma K.K.	July 29, 2009
Tebipenem Pivoxil ORAPENEM FINE GRANULES 10% FOR PEDIATRIC	Meiji Seika Kaisha, LTD.	August 26, 2009
Dutasteride Avolve Capsules 0.5 mg	GlaxoSmithKline K.K.	September 4, 2009
Mirtazapine REFLEX TABLETS 15 mg	Meiji Seika Kaisha, LTD.	September 7, 2009
Mirtazapine REMERON Tablets 15 mg	Schering-Plough K.K.	September 7, 2009
Mometasone furoate Asmanex Twisthaler 100 μg 60 doses	Schering-Plough K.K.	September 14, 2009
Pemetrexed Sodium Hydrate Alimta Injection 100 mg[*3]	Eli Lilly Japan K.K.	September 24, 2009
Aliskiren Fumarate Rasilez Tablets 150 mg	Novartis Pharma K.K.	October 1, 2009
Bimatoprost LUMIGAN OPTHALMIC SOLUTION 0.03%	Senju Pharmaceutical Co., Ltd.	October 5, 2009
Paroxetine hydrochloride hydrate Paxil Tablets 10 mg and 20 mg[*8]	GlaxoSmithKline K.K.	October 16, 2009
Interferon-beta FERON Injections 1 million, 3 million, and 6 million[*9]	Toray Industries, Inc.	October 16, 2009
Ribavirin REBETOL Capsules 200 mg[*10]	Schering-Plough K.K.	October 16, 2009
Voglibose BASEN Tablets 0.2 and BASEN OD Tablets 0.2[*11]	Takeda Pharmaceutical Company Limited	October 19, 2009

*1: An additional indication for “treatment of patients with unresectable hepatocellular carcinoma”

*2: An additional indication for “treatment of patients with cytomegalovirus infections associated with acquired immunodeficiency syndrome, organ transplants (including haemopoietic stem cell transplants), or malignant tumour”

*3: An additional indication for “treatment of patients with unresectable non-small cell lung cancer advanced and recurrent”

*4: An additional indication for “rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention of structural damage of joints)”

*5: An additional indication for “treatment of patients with polyarticular-course juvenile idiopathic arthritis (only for cases which are not adequately responsive to conventional therapies)”

*6: An additional indication for “treatment of growth hormone hyposecretion in adults (restricted to serious cases)”

*7: An additional indication for “treatment of patients with ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders or polycystic ovarian syndrome”

*8: An additional indication for “social anxiety disorder”

*9: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with ribavirin in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy”

*10: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with interferon beta in patients either (1) with elevated blood HCV-RNA levels or (2) who responded poorly to interferon monotherapy or relapsed after interferon monotherapy”

*11: An additional indication for “inhibition of the development of type II diabetes mellitus in patients with abnormal glucose tolerance (only when diet and exercise therapies failed to improve the condition)”