Pharmaceuticals and Medical Devices Safety Information

No. 258 June 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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Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

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

This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

Pharmaceuticals and Medical Devices Safety Information

No. 258 June 2009

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

[Outline of Information]

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

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

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, they are obligated 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

Selective serotonin reuptake inhibitors (SSRIs) and aggression

	Active ingredient	Brand name (name of company)
Active ingredient Brand name (name of company)	Fluvoxamine maleate Paroxetine hydrochloride hydrate Sertraline hydrochloride Milnacipran hydrochloride	Depromel Tablets 25, 50, and 75 (Meiji Seika Kaisha, Ltd.) Luvox Tablets 25, 50, and 75 (Solvay Seiyaku K.K.) Paxil Tablets 10 mg and 20 mg (GlaxoSmithKline K.K.) J Zoloft Tablets 25 mg and 50 mg (Pfizer Japan Inc.) Toledomin Tablets 12.5 mg, 15 mg, 25 mg, and 50 mg (Asahi Kasei Pharma Corporation) Milnacipran hydrochloride Tablets 15 mg "JG" and 25 mg "JG" (Nihon Generic Co., Ltd.) Milnacipran hydrochloride Tablets 15 mg "NP" and 25 mg "NP" (Nipro Pharma Corporation) Milnacipran hydrochloride Tablets 15 mg "NT" and 25 mg "NT" (Nipro Genepha Corporation) Milnacipran hydrochloride Tablets 15 mg "TYK" and 25 mg "TYK" (Taisho Pharm. Ind., Ltd.) Milnacipran HCL Tablets 15 mg "AMEL" and 25 mg "AMEL" (Kyowa Pharmaceutical Industry Co. Ltd.) Milnacipran hydrochloride Tablets 15 mg "Sawai" and 25 mg "Sawai" (Sawai Pharmaceutical Co., Ltd.) Milnacipran HCL Tablets 15 mg "Taiyo" and 25 mg "Taiyo" (Taiyo Pharmaceutical Industry Co., Ltd.) Milnacipran hydrochloride Tablets 15 mg "Towa" and 25 mg "Towa" (Towa Pharmaceutical Co., Ltd.) Milnacipran hydrochloride Tablets 15 mg "Nichi-iko" and 25 mg "Nichi-iko" (Nichi-iko Pharmaceutical Co., Ltd.) Milnacipran hydrochloride Tablets 15 mg "AFP" and 25 mg "AFP" (Alfresa Pharma Corporation)
Therapeutic Category	Psychotropics	
Indications	**Fluvoxamine maleate** Depression, depressed state, obsessive-compulsive disorder, social anxiety disorder **Paroxetine hydrochloride hydrate** Depression, depressed state, panic disorder, and obsessive-compulsive disorder **Sertraline hydrochloride** Depression, depressed state, and panic disorder **Milnacipran hydrochloride** Depression and depressed state	

1. Introduction

A selective serotonin reuptake inhibitor (SSRI) is an antidepressant designed to improve depressive symptoms by selectively acting on a serotonin transporter in serotonin-releasing synapses, thereby inhibiting reuptake of serotonin. Three active ingredients, which are fluvoxamine maleate, paroxetine hydrochloride hydrate, and sertraline hydrochloride, have been approved in Japan and marketed since May 1999, November 2000, and July 2006, respectively. They were used in approximately 820,000 patients/year, 1,230,000 patients/year, and 580,000 patients/year, respectively, between April 2008 and March 2009 (estimated by marketing authorization holders (MAHs)).

A serotonin and noradrenaline reuptake inhibitor (SNRI) is an antidepressant designed to improve depressive symptoms by inhibiting reuptake of serotonin and noradrenaline at the synapse. One active ingredient approved in Japan is milnacipran hydrochloride, launched in October 2000 and used in approximately 380,000 patients/year between April 2008 and March 2009 (estimated by MAH).

MHLW has brought attention to aggression associated with SSRIs or SNRIs, and included psychoneurotic adverse reactions including agitation, irritation (feeling irritated), irritability, excitability, excitement and aggressive reaction in the "Adverse Reactions" section of PRECAUTIONS in package inserts.

Following a recent review of reported adverse reactions of aggression, etc. including harmful behavior to others (including injury) associated with SSRIs or SNRIs, MHLW issued an alert to patients and their families to pay due attention to changes in patient condition during the course of treatment. On May 8, 2009, MHLW required MAHs to revise PRECAUTIONS in package inserts. The details of these safety measures, etc. are described hereinafter.

2. Reported adverse reactions including hostility/aggression and details of safety measures

Summarized in the table below are cases of hostility/aggression (MedDRA) and harmful behavior to others (including injury) among those cases, in SSRI- or SNRI-associated adverse reactions* reported between the day of launch of the respective products and the end of March 2009.

* A summary of these reported adverse reactions is available in materials of Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council (held on May 8, 2009) at http:///www.mhlw.go.jp/shingi/2009/05/dl/s0508-4j.pdf; pages 6–38 (in Japanese).

Name of drug (Nonproprietary name)	Hostility/Aggression, etc. (cases)	Harmful behavior to others (including injury) identified from the clinical course, among Hostility/Aggression, etc.cases (episodes for which causality with the drug could not be denied) (cases)
Fluvoxamine maleate	65	7 (2)
Paroxetine hydrochloride hydrate	173	26 (2)
Sertraline hydrochloride	15	2 (0)
Milnacipran hydrochloride	15	0* (0)

* 4 episodes had the potential to have resulted in harmful behavior to others (including injury) identified from the clinical course.

After a careful review of the 39 cases of harmful behavior to others including injury (including 4 potential episodes associated with milnacipran hydrochloride that could have resulted in harmful behavior) identified from the clinical course, causality between the drug and harmful behavior to others could not be denied in 2 cases of reported adverse reactions associated with fluvoxamine maleate and 2 cases of reported adverse reactions associated with paroxetine hydrochloride hydrate. For the remaining 35 cases of adverse reactions, causality between the drug and adverse reactions was considered unknown.

Regarding reported adverse reactions reviewed for a causal relationship, including those for which causality could not be denied, most patients were in a depressed state of manic depressive psychosis or schizophrenia, or suffered comorbid disorders such as alcoholism and personality disorder when under treatment with SSRIs or SNRIs. Therefore, treatment with SSRIs or SNRIs may have caused excitement, aggression, or irritability or may have exacerbated comorbid disorders, ultimately triggering harmful behavior to others. These findings suggested the necessity for taking patient's condition into due consideration before prescribing SSRIs or SNRIs, and careful administration of these drugs to patients

with manic depressive psychosis or an organic brain disorder, those predisposed to schizophrenia, or those with highly impulsive comorbid disorders.

As reviews showed that whether harmful behavior to others was a result of adverse reactions due to a drug or the exacerbation of comorbid disorders was unknown in most reported cases, it is regarded as necessary to alert patients and their families to pay due attention to changes in patient condition during the course of treatment, as well as risks associated with suicide, regardless of whether harmful behavior to others is related to adverse reactions or exacerbation of the primary disease or comorbid disorders.

Although no harmful behavior to others has been reported in patients treated with milnacipran hydrochloride, some cases could have resulted in harmful behavior to others (including injury), and a review of these cases has revealed a trend similar to that observed in patients treated with SSRIs. Therefore, it was reviewed that milnacipran needs a similar alert as well as SSRI.

In light of the above findings and discussions amongst specialists, it is considered necessary to add the following precautionary statements to the "Important Precautions" section of package inserts: 1) Episodes of anxiety, irritation, excitement, panic attack, irritability, hostility, aggression, and impulsivity have been reported; 2) In patients with these symptoms or behavior, exacerbation of underlying disease, harmful behavior to others, etc. have been reported, though causality with the drugs is not clear; 3) Patients should be carefully monitored for changes in their clinical condition; 4) Patients' families should be given full information on risks associated with changes in behavior such as excitement, aggression, irritability, etc., and an exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

In addition, MHLW has decided that in the section of "Careful Administration", the following sentence was added; patients with organic brain disorders, those predisposed to schizophrenia, and those with highly impulsive comorbid disorders should be admitted with sufficient care.

MHLW will continue deliberations on the appropriate and effective provision of information for medical practice, patients, and their families, in cooperation with the "Committee on Appropriate Use of Antidepressants" (Chairman: Teruhiko Higuchi, President, National Center of Neurology and Psychiatry) established by the Japanese Society of Mood Disorders.

In addition to continuing review of reported adverse reactions associated with SSRIs and SNRIs, MHLW also plans to review reported adverse reactions associated with other types of antidepressants.

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

Fluvoxamine maleate

[Careful Administration] Patients with highly impulsive comorbid disorders

[Important Precautions] Patients with depressive symptoms have suicidal ideation and may attempt suicide. Such patients should be carefully monitored for changes in their clinical condition during early periods of drug therapy or at times of dose changes.
Episodes of anxiety, irritation, excitement, panic attack, insomnia, irritability, hostility, aggression, impulsivity, akathisia/psychomotor restlessness, hypomania and mania have been reported. In patients with these symptoms or behavior, exacerbation of underlying disease, suicidal ideation, suicide attempts, and harmful behavior to others have been reported, though causality with the drug is unknown. Patients should be monitored carefully for changes in their clinical condition, and if exacerbation of any of these symptoms is observed, drug dose should not be increased, and appropriate measures should be taken such as discontinuation of the drug after gradual dose reduction.
Patients' families should be given full information on the risk of suicidal ideation, suicide attempts, changes in behavior such as excitement, aggression, irritability, etc., and exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

Paroxetine hydrochloride hydrate

[Careful Administration] Patients with manic depressive psychosis
Patients with organic brain disorders or those predisposed to schizophrenia
Patients with highly impulsive comorbid disorders

[Important Precautions] Patients with depressive symptoms have suicidal ideation and may attempt

suicide. Such patients should be carefully monitored for changes in their clinical condition during early periods of drug therapy or at times of dose changes.
Patients with psychiatric disorders other than depression and depressed state for which this drug is indicated may also attempt suicide, and may experience further depression or state of depression. These patients should also be carefully monitored during a course of drug therapy.
Episodes of anxiety, irritation, excitement, panic attack, insomnia, irritability, hostility, aggression, impulsivity, akathisia/psychomotor restlessness, hypomania and mania have been reported. In patients with these symptoms or behavior, exacerbation of an underlying disease, suicidal ideation, suicide attempts, and harmful behavior to others have been reported, though causality with the drug is not clear. Patients should be carefully monitored for changes in their clinical condition, and if exacerbation of any of these symptoms is observed, drug dose should not be increased, and appropriate measures should be taken such as discontinuation of the drug after gradual dose reduction.
Patients' families should be given full information on the risk of suicidal ideation, suicide attempts, changes in behavior such as excitement, aggression, irritability, etc., and exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

Sertraline hydrochloride

[Careful Administration]

Patients with manic depressive psychosis
Patients with organic brain disorders or those predisposed to schizophrenia
Patients with highly impulsive comorbid disorders

[Important Precautions]

Patients with depressive symptoms have suicidal ideation and may attempt suicide. Such patients should be carefully monitored for changes in their clinical condition during early periods of drug therapy or at times of dose changes.
Episodes of anxiety, irritation, excitement, panic attack, insomnia, irritability, hostility, aggression, impulsivity, akathisia/psychomotor restlessness, hypomania and mania have been reported. In patients with these symptoms or behavior, exacerbation of an underlying disease, suicidal ideation, suicide attempts and harmful behavior to others have been reported, though causality with the drug is not clear. Patients should be carefully monitored for changes in their clinical condition, and if exacerbation of any of these symptoms is observed, drug dose should not be increased, and appropriate measures should be taken such as discontinuation of the drug after gradual dose reduction.
Patients' families should be given full information on the risk of suicidal ideation, suicide attempts, changes in behavior such as excitement, aggression, irritability, etc., and exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

Milnacipran hydrochloride

[Careful Administration] Patients with highly impulsive comorbid disorders

[Important Precautions] Patients with depressive symptoms have suicidal ideation and may attempt suicide. Such patients should be carefully monitored for changes in their clinical condition during early periods of drug therapy or at times of dose changes.
Episodes of anxiety, irritation, excitement, panic attack, insomnia, irritability, hostility, aggression, impulsivity, akathisia/psychomotor restlessness, hypomania and mania have been reported. In patients with these symptoms or behavior, exacerbation of an underlying disease, suicidal ideation, suicide attempts and harmful behavior to others have been reported, though causality with the drug is not clear. Patients should be carefully monitored for changes in their clinical condition, and if exacerbation of any of these symptoms is observed, drug dose should not be increased, and appropriate measures should be taken such as discontinuation of the drug after gradual dose reduction.
Patients' families should be given full information on the risk of suicidal ideation, suicide attempts, changes in behavior such as excitement, aggression, irritability, etc., and exacerbation of underlying disease, and be instructed to keep in close contact with the physician.

Case Summary

<Fluvoxamine maleate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 20s	Depressed state (None)	50 mg for 7 days ↓ 75 mg for 64 days ↓ 100 mg for 21 days ↓ 150 mg for 25 days	**Aggression** Medical history: neurosis during high school 8 months before administration: The patient experienced a panic disorder with agoraphobia accompanied by depressive symptoms. She initially presented only with panic disorder and later with depression as well, compromising her clinical condition. Amoxapine, ethyl loflazepate, and lofepramine hydrochloride were initially administered without satisfactory outcome. On day 1 of administration: Treatment with this drug was started at 50 mg. Pretreatment symptoms included depressed mood, trouble falling asleep, anxiety, fear, and sudden palpitation. On day 8 of administration: Dose increased to 75 mg. On day 72 of administration: Dose increased to 100 mg. Panic disorder and depressed state remitted but the patient often became irritated and readily got in arguments with her mother. Treatment with sulpiride was added. Addiction to pachinko games and overeating were also noted. On day 116 of administration: The patient physically attacked her husband presumably out of escalating frustration. She was transported to an emergency hospital by ambulance and stayed there overnight. On day 117 of administration (day of discontinuation): The patient was admitted to the psychiatric department to treat the primary disease. This drug was discontinued. Treatment with amoxapine, ethyl loflazepate, and sulpiride was continued. 1 week after discontinuation: Symptoms improved.
	Concomitant medications: ethyl loflazepate, amoxapine and sulpiride			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 20s	Depressed state (None)	75 mg for 10 days ↓ 100 mg for 21 days ↓ 150 mg for 8 days	**Aggression** Approx. 2 years before administration: Administration of amoxapine, sulpiride, and dosulepin hydrochloride was started to treat obsessive-compulsive disorder, panic disorder, phobia, and depressive state. The patient became irritated to the point of taking it out on her husband or mother and throwing objects towards them. Approx. 6 months before administration: Treatment with ethyl loflazepate was started. On day 1 of administration: Treatment with this drug was started at 75 mg. Pretreatment symptoms included depressed mood, trouble falling asleep, agitation, anxiety, tension, fear, palpitation, queasy, and dizziness. On day 11 of administration: Dose increased to 100 mg. On day 32 of administration: Dose increased to 150 mg. On day 39 of administration (day of discontinuation): The patient physically attacked her mother presumably out of escalating frustration. This drug was discontinued. 1 day after discontinuation: Symptoms improved after administration of sulpiride and amoxapine. 7 days after discontinuation: Symptoms remitted. Compulsive-obsessive disorder relatively improved but depressive symptom manifested repeatedly.
	Concomitant medications: ethyl loflazepate, amoxapine, sulpiride and dosulepin hydrochloride			

<Paroxetine hydrochloride hydrate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 60s	Depression (Hypertension, chronic bronchial asthma, hyperuricaemia, and gastritis)	20 mg for 28 days ↓ 40 mg for 43 days	**Confusional state** 87 days before administration: Administration of fluvoxamine maleate and flunitrazepam was started at 100 mg and 1 mg, respectively, to treat depression. The period of sulpiride therapy is unknown. On day 1 of administration: Treatment with this drug was started at 20 mg. Pretreatment symptoms included depressed mood and anxiety. On day 29 of administration: Dose increased to 40 mg. On day 68 of administration: The patient suffered from insomnia, anorexia, and poor concentration and was unable to do the housework. On day 70 of administration: A wide variety of symptoms including insomnia, talkativeness, hyperkinesis, auditory hallucinations, visual hallucinations (close to illusion) manifested, and then mental concentration decreased, defiant behavior, excitement, biting and holding on to an object occurred. On day 71 of administration (day of discontinuation): This drug and fluvoxamine maleate were discontinued. 1 day after discontinuation: The patient was admitted to hospital as her family was unable to handle the above symptoms. Oral treatments were limited to etizolam, kallidinogenase and flunitrazepam, and 2.5 mg each of haloperidol and biperiden lactate were intramuscularly injected, and drip infusion was continued for 3 days while following-up. The patients needed to be confined in a private room for several days. 3 days after discontinuation: The patients started to be able to sleep for a few hours and eat meals gradually, and her psychiatric symptoms gradually improved. 12 days after discontinuation: Patient discharged on condition almost returning to normal.
	Concomitant medications: fluvoxamine maleate, sulpiride, flunitrazepam, kallidinogenase, etizolam, theophylline, ranitidine hydrochloride, allopurinol and inhalant for asthma			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 20s	Depressed state (Schizophrenia)	10 mg for 71 days	**Mania** On day 1 of administration: Administration of this drug was started at 10 mg to treat the depressed state. Pretreatment symptoms included depressed mood and reduced willingness to work. On day 51 of administration: Change to manic state occurred. On day 52 of administration: The patient fought and stabbed a person in the neck on the street in the middle of night. On day 71 of administration (day of discontinuation): This drug was discontinued. Symptoms remitted.
	Concomitant medications: risperidone			

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Important Safety Information

This section presents contents of revisions and the summary of cases 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 April 24, 2009.

1 Isoflurane

Brand name (name of company)	Forane (Abbott Japan Co., Ltd.) Isoflurane "AW" (Air Water Inc.) Escain (Mylan Inc.)
Therapeutic Category	General anesthetics
Indications	General anesthesia

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

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock or anaphylactoid symptoms may occur. Patients should be closely monitored and if any abnormalities including blood pressure decreased, dyspnoea, angioedema (face oedema, laryngeal oedema, etc.), generalized flushing, and urticaria are observed, administration should be discontinued and appropriate measures should be taken.
Hepatitis, hepatic function disorder: Hepatitis or hepatic function disorder with marked elevations of AST (GOT), ALT (GPT), etc. may occur. If any abnormalities are observed, appropriate measures should be taken. Repeated administration in a short period is reported to be associated with increased frequency of these abnormalities. It is therefore preferable that repeated administration at intervals of 3 months or less be avoided. Cross-hypersensitivity between this drug and other halogenated anesthetics has also been reported.

<Reference>

The number of adverse reactions (for which causality could not be denied) reported between April 1991 and March 10, 2009
- Shock, anaphylactoid symptoms: 4 cases (of which 1 had a fatal case)
- Hepatitis, hepatic function disorder: 18 cases (of which 5 had fatal cases)

The number of patients treated with Isoflurane for a year estimated by MAH: approximately 90,000 patients (April 2008 to March 2009)
Marketed in Japan in: April 1990.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 30s	General anesthesia (None)	0.6% Dose unknown For 5 minutes	**Anaphylactic shock (bronchial spasm, cardiac arrest)** Medical history: None Before administration: The patient was transferred to the operating room to undergo cervical disk herniation surgery. Blood pressure 128/84 mmHg; pulse rate 79. Diazepam, droperidol, thiopental sodium, and vecuronium bromide were administered followed by ventilation with 100% oxygen. SaO_2 was 99%. On administration: After endotracheal intubation, inhalation was started with a mixture of 50% oxygen, 50% nitrous oxide, and 0.6% isoflurane. 5 minutes after administration (time of discontinuation): Because decreased blood pressure was observed immediately after inhalation was started, inhalation was discontinued. The patient's posture was subsequently changed and both lungs were auscultated. No particular problems were noted. 5 minutes after discontinuation: Airway pressure increased too high to knead the respirator bag, resulting in inability to ventilate the patient. Aminophylline hydrate and methylprednisolone sodium succinate were administered intravenously. Subsequently, 1 mg of adrenaline was injected into the trachea but ventilation could not be resumed and SaO_2 dropped to the 40s. Chest X-ray was conducted. Marked respiratory distress syndrome was observed for both lungs, while the endotracheal tube remained in the trachea. Inability to ventilate the patient continued, and blood pressure and heart rate dropped further to the 60s and 40s, respectively. 25 minutes after discontinuation: Blood pressure lowered gradually. Cardiac arrest occurred and cardiopulmonary resuscitation was conducted with cardiac massage, administration of adrenaline, sodium bicarbonate, methylprednisolone sodium succinate, ulinastatin, etc., and infusion of adrenaline at 2 mg and betamethasone sodium phosphate into the trachea. Bronchoscopy confirmed that the ET tube was located in the trachea and also revealed marked mucosal oedema accompanied by a large amount of foamy secretion. 55 minutes after discontinuation: A little ventilation became available and heart rate rose to the 40s–80s. Administration of dopamine hydrochloride, a vasopressor, was started and blood pressure and heart rate recovered to 148/62 mmHg and 145, respectively. The patient left the operating room and started to breathe spontaneously. 2 days after discontinuation: Respiratory arrest occurred. The patient was placed on mechanical ventilation. 3 days after discontinuation: Despite mechanical ventilation, the patient died of cardiac arrest.
	Concomitant medications: atropine sulfate hydrate, diazepam, droperidol, thiopental sodium, vecuronium bromide, nitrous oxide			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	General anesthesia (None)	1.5% 5 mL Duration unknown	**Anaphylactic shock** Medical history: Cold urticaria Before administration: No abnormal findings from examinations. The patient was transferred to the operating room to undergo left maxillary epulis resection. Nitrous oxide 4 L, oxygen 4 L, sevoflurane 1.5%, vecuronium bromide 2.0 mg, propofol 120 mg and suxamethonium chloride hydrate 70 mg were administered, followed by oral intubation. A sudden drop in blood pressure and an increase in heart rate as well as precordial flare were observed. Inhalation of sevoflurane and nitrous oxide were discontinued. Blood pressure read 33/24 mmHg. After drip infusion of dopamine hydrochloride 65 mg and hydrocortisone sodium succinate, blood pressure rose and precordial flare almost subsided. On administration: After inhalation of this drug, blood pressure fell again and a tachycardiac tendency and precordial flare were observed. Inhalation of this drug and nitrous oxide was immediately discontinued and continuous drip infusion of dopamine hydrochloride was started simultaneously. 100% oxygen was introduced, and then surgery discontinued. After administration: After confirming the patient's hemodynamic condition was stabilized, she left the operating room. [Examination to determine cause of adverse reactions] This drug and propofol LMIT: false-positive Chemotaxis chamber method: positive
	Concomitant medications: sevoflurane, vecuronium bromide, suxamethonium chloride hydrate, propofol, atropine sulfate hydrate, midazolam, famotidine, nitrous oxide, carbazochrome sodium sulfonate hydrate, conjugated estrogen			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 60s	General anesthesia (Hypertension)	1.0% Dose unknown For 4 hours	**Hepatitis fulminant** On day of administration: After introducing thiamylal sodium 250 mg followed by vecuronium bromide 11 mg for muscle relaxation, a laparoscopic cholecystectomy combined with hernioplasty was performed under anesthesia with isoflurane. The patient fared well from immediately after surgery to 2 days after administration. On 1 day after administration hepatic function was normal, with AST (GOT) 33 IU/L and ALT (GPT) 31 IU/L. 3 days after administration: Lowering of consciousness, delirium, and cold sweat were observed since early morning. Blood pressure dropped to the 50s and BE was -16.0 showing severe acidosis. AST (GOT) 10747 IU/L, ALT (GPT) 5764 IU/L, LDH 25762 IU/L, bleeding tendency, and platelet count $3\times10^4/mm^3$ indicated hepatitis fulminant and DIC. Fresh frozen human plasma and ulinastatin

were administered followed by continuous infusion of gabexate mesilate and catecholamine.
4 days after administration:
The first plasmapheresis was performed. Absence of urination required frequent dosing of diuretics. The patient was fully conscious and was able to communicate.
5 days after administration:
The second plasmapheresis was performed. Urination was absent, BUN 83.4 mg/dL, and creatinine 6.1 mg/dL.
6 days after administration:
The third plasmapheresis was performed, yet organic jaundice progressed. BUN 116 mg/dL, creatinine 7.4 mg/dL.
7 days after administration:
The first dialysis was performed. Urination was absent.
8 days after administration:
The second dialysis was performed. AST (GOT) 110 IU/L, ALT (GPT) 123 IU/L, LDH 2748 IU/L, total bilirubin 13.4 mg/dL, BUN 147 mg/dL, creatinine 8.0 mg/dL.
The patient had atrial fibrillation at night but was fully conscious.
9 days after administration:
The third dialysis was performed. Total bilirubin 58.6 mg/dL. Disturbance of consciousness rapidly progressed and the patient had flapping tremor (++) and fell into hepatic coma. After ECG abnormalities were observed, the patient died.

Clinical Laboratory Values

	14 days before administration	1 day after administration	3 days after administration	4 days after administration	5 days after administration	6 days after administration	8 days after administration	9 days after administration
AST (GOT) (IU/L)	19	33	10747	23034	3318	420	110	66
ALT (GPT) (IU/L)	16	31	5764	8063	1950	432	123	77
AL-P (IU/L)	209	—	172	378	489	357	305	318
LDH (IU/L)	356	—	25762	42526	9774	2976	2748	1852
Total bilirubin (mg/dL)	0.9	1.9	2.9	4.7	8.2	10.1	13.4	58.6
BUN (mg/dL)	19.2	16.5	32.2	47.9	83.4	116	147	97.5
Creatinine (mg/dL)	0.9	0.8	3.1	3.8	6.1	7.4	8.0	4.9

Concomitant medications: cefmetazole sodium, thiamylal sodium, vecuronium bromide, nifedipine, carbazochrome sodium sulfonate hydrate, tranexamic acid, buprenorphine hydrochloride

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Treatment duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/Age</th><th>Reason for use (complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>4</td><td>Female
60s</td><td>General anesthesia
(None)</td><td>Concentration unknown
40 mL
Duration unknown</td><td>Drug-induced hepatitis
10 days before administration:
AST (GOT) 23 IU/L, ALT (GPT) 26 IU/L.
Day of administration:
The patient inhaled this drug before undergoing surgery on cervical spondylotic myelopathy.
1 day after administration:
Blood examination confirmed hepatic function disorder with AST (GOT) 2040 IU/L and ALT (GPT) 2965 IU/L.
5 days after administration:
Drip infusion of 500 mL of acetated Ringer solution, glycyrrhizic acid preparation, and liver extract/flavin-adenine dinucleotide was started twice daily.
10 days after administration:
Drip infusion therapy was ended.
25 days after administration:
AST (GOT) and ALT (GPT) recovered to 25 IU/L and 41 IU/L, respectively.</td></tr>
<tr><td colspan="5">Clinical Laboratory Values
<table>
<tr><th></th><th>10 days before administ-ration</th><th>1 day after administ-ration</th><th>2 days after administ-ration</th><th>4 days after administ-ration</th><th>8 days after administ-ration</th><th>11 days after administ-ration</th><th>25 days after administ-ration</th></tr>
<tr><td>AST (GOT) (IU/L)</td><td>23</td><td>2040</td><td>2431</td><td>399</td><td>157</td><td>45</td><td>25</td></tr>
<tr><td>ALT (GPT) (IU/L)</td><td>26</td><td>2965</td><td>4115</td><td>2220</td><td>759</td><td>326</td><td>41</td></tr>
<tr><td>AL-P (IU/L)</td><td>292</td><td>290</td><td>295</td><td>366</td><td>931</td><td>963</td><td>–</td></tr>
<tr><td>LDH (IU/L)</td><td>196</td><td>1807</td><td>1381</td><td>347</td><td>221</td><td>187</td><td>141</td></tr>
<tr><td>Total bilirubin (mg/dL)</td><td>0.64</td><td>1.09</td><td>1.01</td><td>1.43</td><td>0.71</td><td>0.48</td><td>0.49</td></tr>
</table></td></tr>
<tr><td colspan="5">Concomitant medications: mecobalamin, limaprost alfadex, famotidine, brotizolam, electrolyte infusion, methylprednisolone sodium succinate, cefmetazole sodium, atropine sulfate hydrate, midazolam, thiamylal sodium, vecuronium bromide, neostigmine methylsulfate, pentazocine, ephedrine hydrochloride, lidocaine hydrochloride, adrenaline, carbazochrome sodium sulfonate hydrate, tranexamic acid, acetated Ringer solution containing glucose, pantethine, flurbiprofen axetil</td></tr>
</table>

3

Revision of PRECAUTIONS

(No. 206)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated April 24, 2009 (excluding those presented in "2. Important Safety Information" of this Bulletin).

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1 <Antihypertensives>

Olmesartan medoxomil

[Brand Name]	Olmetec Tablets 5 mg, 10 mg, and 20 mg (Daiichi-Sankyo Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Thrombocytopenia:** Thrombocytopenia may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Hypoglycaemia**: Hypoglycaemia may occur (particularly in patients being treated for diabetes). Patients should be carefully monitored and if feelings of weakness, feelings of hunger, cold sweat, trembling of hands, mental concentration decreased, convulsion, or consciousness disturbed is observed, administration should be discontinued and appropriate measures should be taken.

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2 <Hemostatics>

Oxidized cellulose

[Brand Name]	SURGICEL Absorbable Hemostat (Johnson & Johnson K.K.)
[Contraindications]	Placement around a bone tunnel, bone border, around the spinal cord, optic nerves or optic chiasm. Placement on the fracture surface or laminectomy wounds.
[Precautions of dosage and administration]	In case of following hemostasis assist, this product should be removed on achieving hemostasis: 1) To assist hemostasis around a bone tunnel, bone border, laminectomy wounds, around the spinal cord, optic nerve, or optic chiasm. 2) To assist hemostasis during lung lobectomy or repair of frontal bone fracture. 3) To assist hemostasis on the fracture surface.
[Adverse reactions (clinically significant adverse reactions)]	**Bone regeneration inhibition:** When this product is placed on the fracture surface, it may inhibit bone regeneration and cause cyst formation. **Neuropathy:** Neuropathy due to compression by swelling of this product may occur. **Visual impairment:** Visual impairment due to compression by swelling of this product may occur.

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3 <Antineoplastics-Miscellaneous>
Toremifene citrate

[Brand Name]	Fareston Tablets 40 and 60 (Nippon Kayaku Co., Ltd.) and other
[Contraindications]	Patients with prolonged QT interval or with a history of prolonged QT interval (including congenital long QT syndrome) Patients with hypokalaemia Patients on treatment with antiarrhythmic agents of Class IA (quinidine, procainamide, etc.) or Class III (amiodarone, sotalol, etc.)
[Careful Administration]	Patients with heart disorder prone to arrhythmia due to severe bradycardia or myocardial ischaemia
[Important Precautions]	This drug was reported to cause QT interval prolongation. Caution should be exercised to the cardiovascular condition before this drug is administered to patients with cardiovascular disorders.
[Interactions (contraindications for concomitant use)]	Antiarrhythmic agents of Class IA (quinidine, procainamide, etc.) or Class III (amiodarone, sotalol, etc.)

4 <Antineoplastics-Miscellaneous>
Sorafenib tosilate

[Brand Name]	Nexavar Tablet 200 mg (Bayer Yakuhin, Ltd.)
[Important Precautions]	Hand and foot syndrome, exfoliative dermatitis, oculomucocutaneous syndrome (Stevens-Johnson syndrome), or erythema multiforme may occur. Patients should be instructed to consult a dermatologist as necessary. Leukopenia, neutropenia, lymphopenia, thrombocytopenia, or anaemia may occur. Patients should be periodically examined for hematology including differential white blood counts and carefully monitored for infection, bleeding tendency, etc.
[Adverse reactions (clinically significant adverse reactions)]	**Hand and foot syndrome, exfoliative dermatitis**: Hand and foot syndrome or exfoliative dermatitis may occur. If any skin symptoms develop, symptomatic treatment, dose reduction or temporary or permanent drug withdrawal should be considered. **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) or erythema multiforme may occur. Patients should be carefully monitored and if any of these events is suspected, administration should be discontinued and appropriate measures should be taken. **Leukopenia, neutropenia, lymphopenia, thrombocytopenia, anaemia**: Leukopenia, neutropenia, lymphopenia, thrombocytopenia or anaemia may occur. Patients should be carefully monitored and if any abnormalities are observed, the dose should be reduced or administration should be temporarily or permanently discontinued and appropriate measures should be taken.

4

List of products subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug . It is imposed that its Marketing Authorization Holder collects the adverse drug rections (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 June 1, 2009)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Pirfenidone Pirespa Tablets 200 mg	Shionogi & Co., Ltd.	December 12, 2008
Lamotrigine Lamictal Tablets 2 mg, 5 mg, 25 mg, and 100 mg	GlaxoSmithKline K.K.	December 12, 2008
Tafluprost TAPROS ophthalmic solution 0.0015%	Santen Pharmaceutical Co., Ltd.	December 16, 2008
Phenobarbital Sodium NOBELBAR 250 mg for Injection	Nobelpharma Co., Ltd.	December 16, 2008
Haemophilus influenzae type b conjugate vaccine ActHIB	Sanofi Pasteur-Daiichi Sankyo Vaccine Co., Ltd.	December 19, 2008
Thyrotropin Human Alfa (genetical recombination) THYROGEN IM Injection 0.9 mg	Sato Pharmaceutical Co., Ltd.	January 13, 2009
Etravirine INTELENCE Tablets 100 mg	Janssen Pharmaceutical K.K.	January 19, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 100 Diskus *1	GlaxoSmithKline K.K.	January 21, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 250 Diskus *2	GlaxoSmithKline K.K.	January 21, 2009
Ganirelix Acetate Ganirest Subcutaneous 0.25mg Syringe	Schering-Plough K.K.	January 22, 2009
Maraviroc CELSENTRI Tablets 150 mg	Pfizer Japan Inc.	January 22, 2009
Dasatinib Hydrate SPRYCEL Tablets 20 mg and 50 mg	Bristol Myers K.K.	February 2, 2009
Estradiol·Norethisterone Acetate MENOAID COMBIPATCH	ASKA Pharmaceutical Co., Ltd.	February 5, 2009
Thalidomide THALED capsule 100	Fujimoto Pharmaceutical Corporation	February 6, 2009
Nilotinib Hydrochloride Hydrate TASIGNA Capsules 200 mg	Novartis Pharma K.K.	February 16, 2009

Estradiol·Levonorgestrel Wellnara	Bayer Yakuhin, Ltd.	February 17, 2009
Botulinum toxin type A BOTOX Vista Injection 50 Units	GlaxoSmithKline K.K.	February 23, 2009
Enoxaparin Sodium Clexane for Subcutaneous Injection Kit 2000 IU [*3]	Sanofi-Aventis K.K.	February 23, 2009
Lanthanum Carbonate Hydrate Fosrenol Chewable Tablets 250mg and 500mg	Bayer Yakuhin, Ltd.	March 11, 2009
Omalizumab（Genetical Recombination） Xolair for s.c. injection	Novartis Pharma K.K.	March 13, 2009
Candesartan Cilexetil / Hydrochlorothiazide ECARD Combination Tablets LD, ECARD Combination Tablets HD	Takeda Pharmaceutical Company Limited	March 13, 2009
Zonisamide TRERIEF Tablets 25mg	Dainippon Sumitomo Pharma Co., Ltd.	March 13, 2009
Valsartan/Hydrochlorothiazide Co-DIO Combination Tablets MD, Co-DIO Combination Tablets EX	Novartis Pharma K.K.	March 13, 2009
Ranibizumab（Genetical Recombination） LUCENTIS solution for intravitreal injection 2.3mg/0.23mL	Novartis Pharma K.K.	March 13, 2009
Nalfurafine Hydrochloride REMITCH CAPSULES 2.5μg	Toray Industries, Inc.	March 24, 2009
Azithromycin Hydrate ZITHROMAC SR Dry Syrup 2g for Adults	Pfizer Japan Inc.	April 6, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 50 Air 120 puffs	GlaxoSmithKline K.K.	April 6, 2009
Minodronic Acid Hydrate Bonoteo Tablets 1mg	Astellas Pharma Inc.	April 7, 2009
Minodronic Acid Hydrate RECALBON Tablets 1mg	Ono Pharmaceutical Co., Ltd.	April 7, 2009
Cetirizine Hydrochloride Zyrtec Dry Syrup 1.25%, Zyrtec tablets 5mg [*1]	UCB Japan Co. Ltd	April 22, 2009
Somatropin (genetical recombination) NORDITROPIN S injection 5mg and 10mg, Norditropin NordiFlex injection 5mg, 10mg and 15mg [*4]	Novo Nordisk Pharma Ltd.	April 22, 2009
Doxorubicin Hydrochloride DOXIL Injection 20mg [*5]	Janssen Pharmaceutical K.K.	April 22, 2009
Sodium Chloride/Potassium Chloride/Sodium Bicarbonate/Anhydrous Sodium Sulfate Niflec for internal use [*6]	Ajinomoto Pharma Co., Ltd.	April 22, 2009
Mosapride Citrate Gasmotin Tablets 2.5 mg and 5 mg, Gasmotin Powder [*7]	Dainippon Sumitomo Pharma Co., Ltd.	April 22, 2009
Sorafenib Tosilate Nexavar Tablets 200mg	Bayer Yakuhin, Ltd.	May 20, 2009

Valganciclovir Hydrochloride VALIXA Tablets 450mg	Mitsubishi Tanabe Pharma Corporation	May 20, 2009
Pemetrexed Sodium Hydrate Alimta Injection 500mg	Eli Lilly Japan K.K.	May 20, 2009

*1: An additional administration for "pediatrics"

*2: An additional indication for "remission of various symptoms of chronic obstructive pulmonary disease (COPD) (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 stimulant)"

*3: An additional indication for "prophylaxis of venous thromboembolisms in patients undergoing abdominal surgery who are at risk for thromboembolic complications"

*4: An additional indication for "replacement of endogenous growth hormone in adults with growth hormone hyposecretion (restricted to serious cases)"

*5: An additional indication for "treatment of patients with ovarian cancer whose disease has progressed after chemotherapy"

*6: An additional indication for "cleansing of the colon as a preparation prior to radiographic contrast barium enema"

*7: An additional indication for "adjunction with colonic cleansing agent for a preparation prior to radiographic contrast barium enema"

*8: An additional indication for "treatment of patients with unresctable hepatocellular carcinoma"

*9: 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"

*10: An additional indication for "treatment of patients with unresctable non-small cell lung cancer recurrent and advanced"

Reference 1. Project for promoting safe use of drugs

With the aim of promoting implementation of a prediction and prevention style as safety measures, the MHLW has been conducting a 2-year project for promoting the safe use of drugs since 2007, to promote effective practical use of safety information for the avoidance of adverse drug reactions in clinical practice. The Japanese Society of Hospital Pharmacists has participated in this project and recently submitted a report, which is presented hereinafter. The full text of the report including case reports is available at the MHLW website and the pharmaceuticals and medical devices information website.

The MHLW website
(http://www.mhlw.go.jp/shingi/2009/05/s0501-3.html)
The pharmaceuticals and medical devices information website
(http://www.info.pmda.go.jp/kyoten_iyaku/report_case.html)

Reference 2. Manuals for Management of Individual Serious Adverse Drug Reactions

Manuals for Management of Individual Serious Adverse Drug Reactions have been presented in Pharmaceuticals and Medical Devices Safety Information No. 230, No. 237 and No. 246. As of May 2009, manuals including "retinal and visual pathway disorders," etc. were finalized and available at the MHLW website and the pharmaceuticals and medical devices information website.

The manual titles and common initial symptoms in newly published the Manuals for Management of Individual Serious Adverse Drug Reactions are shown in **Table 1**, and the list of manuals (including those at drafting stage) is shown in **Table 2**.

It is hoped that these manuals will be used by healthcare providers including physicians, dentists and pharmacists as well as patients to achieve early recognition and prompt response to serious adverse reactions.

Table 1 Manuals for Management of Individual Serious Adverse Drug Reactions released in May 2009

Manual title (adverse drug reaction)	Common initial symptoms
Retinal and visual pathway disorders	"Visual acuity decreased," "Difficulty in focusing on a close object," "Difficulty in differentiating colors," "Difficulty in adjusting the eyesight in dim light," "Visual field constriction," "Invisible area existing in the visual field," "Glimmer in the visual field," "Contorted vision"
Glaucoma	"Ocular hyperaemia," "Eye pain," "Cloudy vision," "Headache/feeling queasy," "Invisible area existing in the visual field," "Visual field constriction"
Pulmonary oedema	"Respiratory discomfort," "Whistling sound in the lungs," "Cough/sputum," "Breathing rate increased," "pulse quickens"
Pleurisy, pleural effusion	"Respiratory discomfort," "Chest pain"
Hyperglycaemia	"Thirst," "Excessive drinking," "Polyuria," "Weight decreased"
Acute generalized exanthematous pustulosis	"Hyperthermia (38°C or above)," "Redness over large part of the skin," "Microcysts on the reddened skin," "General malaise," "anorexia"
Peripheral nerve disorder	"Numbness in hands and feet," "Tingling in hands and feet," "Sensory loss in hands and feet," "Weakness in hands and feet," "Difficulty in grasping an object," "Frequent tripping in walking," "Inability to stand up from a sitting position," "Inability to go up stairs"
Guillain-Barre syndrome (acute inflammatory demyelinating polyradiculoneuropathy, acute inflammatory demyelinating polyradiculoneuritis)	"Weakness in both hands and feet," "Tripping in walking," "Inability to go up stairs," "Difficulty in grasping an object," "Decreased sensation in hands and feet," "Facial paralysis," "Difficulty in swallowing," "Respiratory discomfort"
Dyskinesia	"Repeated pursing of lips," "Movement of the tongue from side to side," "Mumbling motion of the mouth," "Pouting of the mouth," "clenching of the jaws," "Once the eyes are closed, they remain tightly closed with wrinkles and are hard to open," "Uncontrolled movement of hands," "Difficulty in walking because of uncontrolled movement of legs," "Inability to relax hands," "Difficulty in walking because of stiff legs"
Convulsion, epilepsy	"Twitching of the face, arms, and legs," "Temporarily decreased consciousness," "Stiffness and shaking of arms and legs"
Bisphosphonate-induced osteonecrosis of jaw	"Pain in the mouth, particularly persistent pain after

Manual title (adverse drug reaction)	Common initial symptoms
	tooth extraction," "White or gray hard stuff jutting from the gum," "Swelling of jaws," "Numbness of the lower lip," "Tooth becoming loose and coming out spontaneously"
Drug-induced stomatitis	"Hyperthermia (38°C or above)," "Ocular hyperaemia," "Soreness inside the mouth and of lips," "Throat pain," "Redness over large part of the skin"
Anticancer drug-induced stomatitis	"Soreness inside the mouth, bleeding, biting sensation when eating hot or cold food/drink," "Dry mouth, redness or swelling inside the mouth," "Difficulty in moving the mouth," "Difficulty in swallowing," "Change in taste"
Thyrotoxicosis	"Palpitation (fast beating)," "Tachycardia (quick pulse)," "Tremor finger," "Loss of weight in spite of normal appetite," "Heavy sweating, sensitive to heat," "General malaise (feeling dull)," "Fatigability (getting tired easily)," "Nervous and agitated," "Slight fever"
Hypothyroidism	"Swelling of anterior neck," "Lack of spirit," "Getting tired easily," "Swelling of eyelids," "Sensitive to cold," "Weight increased," "Slow movement," "Always sleepy," "Poor memory," "Constipation," "Cracking voice"
Acute pancreatitis (drug-induced pancreatitis)	"Sudden stomachache," "Feeling queasy," "Vomiting," "Abdominal pain intensifies when throwing the head back and weakens when bending down"
Ventricular tachycardia	"Dizziness," "Palpitation," "Chest pain," "Chest discomfort"
Cardiac failure congestive	"Respiratory discomfort while moving," "Getting tired easily," "Swelling of legs," "Sudden weight gain," "Cough and pink sputum"
Osteoporosis	"Body height decreased by 2 cm or greater," "Rounded back"
Urinary retention, dysuria	"Urinary hesitation," "Urinary weakness," "Frequent disruptions during urination," "Urinary slowness," "Need to put stress on the abdomen to urinate," "Feeling of residual urine"

Table 2 List of the Manuals for Management of Individual Serious Adverse Drug Reactions (including those at drafting stage) (As of June 2009)

Field	Name of cooperating society	Covered adverse drug reaction
Dermatologicals	The Japanese Dermatological Association	○ Stevens-Johnson syndrome (Oculomucocutaneous syndrome) ○ Toxic epidermal necrosis (Toxic epidermal necrolysis) (Lyell syndrome, Drug eruption Lyell syndrome type) ○ Drug-induced hypersensitivity syndrome ☆ Acute generalized exanthematous pustulosis Dermatitis contact
Hepatic	The Japan Society of Hepatology	○ Drug-induced hepatic disorder (hepatocellular-type drug-induced liver disorder, Cholestasis-type drug-induced liver disorder, Mixed-type Drug-induced liver disorder, Acute hepatic failure, other drug-induced liver disease)
Renal	The Japanese Society of Nephrology	○ Acute renal failure ○ Nephritis interstitial (Tubulointerstitial

		nephritis） Nephrotic syndrome Pyelonephritis Nephrogenic diabetes insipidus Tumour lysis syndrome
Blood	The Japanese Society of Hematology	○ Aplastic anaemia （Pancytopenia） ○ Bleeding tendency ○ Drug-induced anaemia （Haemolytic anaemia, Methaemoglobinaemia, Aplasia pure red cell, Sideroblastic anaemia, Anaemia megaloblastic） ○ Agranulocytosis （Granulocytopenia, Neutropenia） ○ Thrombocytopenia ○ Thrombosis （Thromboembolism, Embolism, Infarction） ○Disseminated intravascular coagulation （Systemic hypercoagulative disorder, Consumption coagulopathy） ○ Disseminated intravascular coagulation （Systemic hypercoagulative disorder, Consumption coagulopathy） Thrombotic thrombocytopenic purpura Heparin-induced thrombocytopenia
Respiratory system	The Japanese Respiratory Society	○ Interstitial pneumonia （Pneumonitis, Alveolitis, Pulmonary fibrosis） ○ Asthmatic attack due to nonsteroidal anti-inflammatory drug （Aspirin asthma, analgesics-induced asthma, aspirin intolerant asthma, Analgesic asthma syndrome） ○ Acute lung injury/Acute respiratory distress syndrome（Acute respiratory distress syndrome）,（Adult respiratory distress syndrome（Adult respiratory distress syndrome）） ☆Pulmonary oedema ☆Pleurisy, Pleural effusion Acute eosinophilic pneumonia Pulmonary alveolar haemorrhage
Alimentary tract	The Japanese Society of Gastroenterology	○ Ileus paralytic ○ Peptic ulcer （Gastric ulcer, Duodenal ulcer, Acute gastric mucosal lesion, NSAIDs-induced ulcer） ○ Pseudomembranous colitis ☆Pancreatitis acute（drug-induced Pancreatitis） Severe diarrhoea
Cardiovascular system	The Japanese Circulation Society	☆Ventricular tachycardia ☆Cardiac failure congestive
Nervous and musculo-skeletal system	The Japanese Society of Neurology	○ Drug-induced parkinsonism ○ Rhabdomyolysis ○ Leukoencephalopathy ☆Peripheral neuropathy ☆Guillain-Barre syndrome(Acute inflammatory demyelinating polyradiculoneuropathy, Acute inflammatory demyelinating

		polyneuropathy) ☆Dyskinesia ☆Convulsion/Epilepsy Meningitis aseptic Acute disseminated encephalomyelitis Ataxia Headache
Psychiatric	The Japanese Society of Clinical Neuropsychopharmacology	○ Neuroleptic malignant syndrome ○ Drug-induced depression Akathisia Serotonin syndrome/Tremor
	The Japan Pediatric Society	Drug withdrawal syndrome neonatal
Metabolism and endocrine	The Japan Endocrine Society	○ Pseudoaldosteronism ☆Thyrotoxicosis ☆Hypothyroidism
	The Japan Diabetes Society	☆Hyperglycaemia Hypoglycaemia
Hypersensitivity	The Japanese Society of Allergology	○ Anaphylaxis ○ Angioedema (Angioneurotic edema) ○ Laryngeal oedema ○ Urticaria/Angiooedema due to nonsteroidal anti-inflammatory drug
Sensory organs (visual)	The Japanese Ophthalmological Society	☆Retinal disorder/Visual field defects ☆Glaucomas
Sensory organs (auditory)	The Oto-Rhino-Laryngological Society of Japan, Inc.	Deafness
Sensory organs (mouth)	The Japanese Stomatological Society	Taste disorders
Oral cavity	The Japanese Society of Oral and Maxillofacial Surgeons	☆Osteonecrosis of jaw due to bisphosphonates ☆Drug-induced stomatitis ☆Stomatitis due to anticancer agents
Bones	The Japanese Orthopaedic Association	☆Osteoporosis
Urinary organs	The Japanese Urological Association	☆Urinary retention /dysuria Cystitis haemorrhagic
Ovary	The Japan Society of Obstetrics and Gynecology	Ovarian hyperstimulation syndrome
Carcinoma	The Japan Society of Clinical Oncology	hand and foot syndrome

Note) Manuals with "○" have already published before, and those with "☆" have newly published recently.

Reference 3. Extension of cooperating hospitals in the project for "Japan Drug Information Institute in Pregnancy"

The Japan drug information institute in pregnancy provides and coordinates teratology information service as described in "Pharmaceuticals and Medical Devices Safety Information" No. 235 and No.246. From current fiscal year, the institute has gained collaboration from three newly added cooperating hospitals (providing consultation using the documents prepared by the Japan drug information institute in pregnancy) to strengthen the system for consultation and collecting information regarding pregnancy and drugs for user's further convenience. Names of the cooperating hospitals are presented below.

[Information on "Japan Drug Information Institute in Pregnancy" and cooperating hospitals]

"Japan Drug Information Institute in Pregnancy" − Setagaya-ku, Tokyo
in National Center for Child Medical Health and Development (NCCHD)
URL: http://www.ncchd.go.jp/kusuri/index.html

(Cooperating hospitals) ○Joined since 2007 ◉Joined since 2008 ☆Joined since 2009

◉ Hokkaido University Hospital − Sapporo-city, Hokkaido

☆ Iwate Medical University Hospital−Morioka-city, Iwate

○ National Hospital Organization Sendai Medical Center − Sendai-city, Miyagi
URL: http://www.snh.go.jp/Medicine/index.html

○ Tsukuba University Hospital − Ttsukuba-city, Ibaraki

○ Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital − Minato-ku, Tokyo

○ St. Luke's International Hospital − Chuo-ku, Tokyo

◉ Japanese Red Cross Nagoya First Hospital − Nagoya-city, Aichi

☆National Hospital Organization Nagara Medical Center −Gifu-city, Gifu

◉ National Hospital Organization Kanazawa Medical Center − Kanazawa-city, Ishikawa

◉ Nara Medical University Hospital − Kashihara-city, Nara

○ Osaka Medical Center and Research Institute for Maternal and Child Health − Izumi-city, Osaka
URL: http://www.mch.pref.osaka.jp/osirase/ninshin/index.html

☆National Hospital Organization Kagawa Children's Hospital− Zentsuji-city, Kagawa

◉ Hiroshima University Hospital − Hiroshima-city, Hiroshima

◉ Kyushu University Hospital − Fukuoka-city, Fukuoka