Pharmaceuticals and Medical Devices Safety Information

No. 242 December 2007

Table of Contents

This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. 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).

Published by
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

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. 242 November 2007

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

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

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 October 31, 2007.

1 Atorvastatin Calcium Hydrate

Brand Name (name of company)	Lipitor Tablets 5 mg and 10 mg (Astellas Pharma Inc.)
Therapeutic Category	Hyperlipidaemia agents
Indications	Hypercholesterolaemia Familial hypercholesterolaemia

≪**PRECAUTIONS** (underlined parts are additions)≫

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, pancytopenia, thrombocytopenia: Agranulocytosis, pancytopenia and thrombocytopenia may occur. Patients should be carefully monitored through periodic testing etc. If abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 2004 to September 2007) (events for which a causality to the drug could not be denied)
• Agranulocytosis: 5 cases (of which 1 had a fatal case)
• Pancytopenia: 1 case (no fatal case)
The number of patients treated with Atorvastatin for a year estimated by MAH (Marketing Authorisation Holder): approximately 2.3 million (2006)
Marketed in Japan in: May 2000

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Hyperlipidaemia (glomerulonephritis chronic, aortic valve stenosis)	20 mg 33 days	**Agranulocytosis** Approx. 5 years before administration: Follow-up was initiated due to unknown renal failure chronic. The patient was considered to have hypertensive nephropathy or glomerulonephritis chronic. Approx. 3 years and 11 months before administration: The patient underwent operation for internal shunt. Approx. 3 years and 8 months before administration: Dialysis started. The patient was maintained on haemodialysis 3 times per week. Approx. 2 months before administration: Aortic valve replacement operation was performed for aortic valve stenosis.

				On day 1 of administration: Administration of 20 mg of this drug was initiated. Prior to the medication on the day, the patient was on treatment with 1.5 g/day of precipitated calcium carbonate, 300 mg/day of rebamipide, 15 mg/day of lansoprazole, 3 mg/day of warfarin potassium, 40 mg/day of isosorbide dinitrate and 24 mg/day of sennoside. On day 27 of administration: White blood cell decreased (granulocytopenia). On day 30 of administration: The patient experienced diarrhoea from around this time. On day 33 of administration (day of discontinuation): Pyrexia of 39°C, malaise and hiccups developed. The patient received emergency outpatient consultation in the afternoon. Detailed examination suggested that he may have severe infectious disease. He was emergently hospitalized. Pneumonia, sepsis, DIC, hepatic function disorder developed. Administration of 500 mg/day of panipenem/betamiprom, 50 mg/day of micafungin sodium and 5 g/day of polyethylene glycol treated human normal immunoglobulin for pneumonia and sepsis was initiated. Administration of 75 μg/day of filgrastim (genetical recombination) was initiated for granulocytopenia. Respiratory status worsened and emergency dialysis was performed the same day. Administration of this drug was discontinued. Chest X-rays, chest CT: Pneumonia Abdominal X-rays, abdominal CT: No abnormal findings Blood culture: Gram-negative bacillus (Escherichia coli etc.) 1 day after discontinuation: Since Gram-negative bacteria were present in a blood culture, endotoxin adsorption therapy was initiated. In an aspiration bone marrow that was performed the same day, an image of self-phagocytosis of blood stem cells was obtained, and the patient was diagnosed with hemophagocytic syndrome. Administration of steroids was initiated. After dialysis, hyperbaric oxygen treatment for severe infectious disease was concomitantly given. Platelets count decreased and FDP increased were confirmed and administration of nafamostat mesilate was initiated with diagnosis of DIC. He maintained remission state during the night. Results of consultation from department of cardiovascular internal medicine: Replaced valve is being favorably maintained. Another CT detected no abnormal findings including intestinal oedema, excluding that the source of the infection is the intestine. Speech impairment was also confirmed. Head and neck CT detected no abnormalities. 2 days after discontinuation: The patient had respiratory arrest in the morning. Cardiopulmonary resuscitation failed, and he died.
	Concomitant medications: precipitated calcium carbonate, rebamipide, lansoprazole, warfarin potassium, isosorbide dinitrate, sennoside, dimemorfan phosphate, carbocisteine, nifedipine			

Clinical Laboratory Values

		42 days before administration	On day 1 of administration	On day 27 of administration	On day 33 of administration (day of discontinuation)	1 day after discontinuation
WBC (/mm^3)		3300	6600	1700	300	200
RBC ($\times 10^4$/mm^3)		306	309	259	253	244
Haemoglobin (g/dL)		10.3	9.7	8.4	8.3	7.9
Haematocrit (%)		30.7	29.4	24.4	24.1	23.9
PLT ($\times 10^4$/mm^3)		13.9	33.9	23.7	11.8	5.6
Neutrophils (%)		59.4	59.1	34.7	2.8	2.9
Eosinophils (%)		6.1	9.4	15.2	4.3	15.7
Basophils (%)		0.1	0.5	0.6	0.4	0.5
Monocytes (%)		3.4	8.3	0.6	2.8	0.4
Lymphocytes (%)		29.4	20.7	47.1	86.9	76.8
CRP (mg/dL)		—	—	—	24.06	—
Total bilirubin (mg/dL)		0.26	0.32	0.23	1.13	2.44
Direct bilirubin (mg/dL)		0.06	—	0.06	—	—
AI-P (IU/L)		252	519	351	414	—
AST (GOT) (IU/L)		10	36	21	108	581
ALT (GPT) (IU/L)		5	13	16	36	220
γ-GTP (IU/L)		35	137	106	208	—
LDH (IU/L)		143	253	211	283	967
CK (CPK) (IU/L)		—	42	—	1844	905
BUN (mg/dL)	Before dialysis	53	35	62	74	—
	After dialysis	22	—	28	—	—
Creatinine (mg/dL)	Before dialysis	10.21	8.87	10.29	10.35	—
	After dialysis	4.81	—	5.20	—	—
Sodium (mEq/L)	Before dialysis	137	138	135	131	134
	After dialysis	138	—	135	—	—
Potassium (mEq/L)	Before dialysis	4.7	5.2	4.3	5.8	5.1
	After dialysis	3.4	—	3.5	—	—
Chloride (mEq/L)	Before dialysis	99	99	99	94	93
	After dialysis	100	—	95	—	—
Blood sugar (mg/dL)		—	—	—	112	—
Total cholesterol (mg/dL)		177	—	196	—	132
TG (mg/dL)		80	170	138	88	—
Pt (seconds)		—	22.1	—	—	28.2
Pt (%)		—	37	—	—	26
β-D-glucan (pg/mL)		—	—	—	—	24.2
Endotoxins (pg/mL)		—	—	—	—	117.0

WBC: White Blood Cell
RBC: Red Blood Cell
PLT: Platelet
CRP: C-Reactive Protein
AI-P: Alkaline Phosphatase
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
γ-GTP: γ-Glutamyltranspeptidase
LDH: Lactate Dehydrogenase
CK: Creatine Kinase
BUN: Blood Urea Nitrogen
TG: Triglyceride
Pt: Prothrombin Time

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Hyperlipidaemia (hypertension, diabetes mellitus)	10 mg 49 days	**Pancytopenia** On day 1 of administration: Administration of 5 mg of enalapril maleate and 10 mg of this drug for hypertension and hyperlipidaemia was initiated. On day 22 of administration: Red blood cell count, haemoglobin and hematocrit decreased to 341 × 10^4/mm^3, 10.2 g/dL and 28.6%, respectively. White blood cell count was 4300/mm^3 and platelet count was 16.9 × 10^4/mm^3. On day 49 of administration (day of discontinuation): Drug-induced pancytopenia was suspected, and administration of enalapril maleate and this drug was discontinued. Administration of 2.5 mg of amlodipine besilate was initiated. 14 days after discontinuation: White blood cell count, red blood cell count and platelet count recovered to 6400/mm^3, 468 × 10^4/mm^3 and 24.4 × 10^4/mm^3, respectively. 22 days after discontinuation: Administration of amlodipine besilate was discontinued, and administration of 5 mg of enalapril maleate was reinitiated. 78 days after discontinuation: Administration of fluvastatin sodium was initiated.
	Concomitant medications: enalapril maleate			

Clinical Laboratory Values

	13 days before administration	On day 22 of administration	On day 36 of administration	14 days after discontinuation	29 days after discontinuation	92 days after discontinuation
WBC (/mm^3)	6000	4300	2800	6400	5400	6600
RBC (×10^4/mm^3)	452	341	314	468	446	447
Haemoglobin (g/dL)	12.8	10.2	10.9	13.9	13.5	13.9
Haematocrit (%)	39.9	28.6	30.3	39.1	38.0	38.1
PLT (×10^4/mm^3)	29.5	16.9	12.0	24.4	26.2	26.4

WBC: White Blood cell
RBC: Red Blood Cell
PLT: Platelet

2 Tizanidine Hydrochloride

Brand Name (name of company)	Ternelin Granules 0.2%, Ternelin Tablets 1mg (Novartis Pharma K.K.) Astonelin Tablets 1 mg (Choseido Pharmaceutical Co., Ltd.) Enchinin Tablets 1 (Medisa Shinyaku Inc.) Gibonz Tablets 1 mg (Kyorin Rimedio Co., Ltd.) Zanpeak Granules 0.2% (Tatsumi Kagaku Co., Ltd.) Sevretin Tablets 1 mg (Nipro Pharma Corporation) Tizanin Granules 0.2%, Tizanin Tablets 1 mg (Nichi-iko Pharmaceutical Co., Ltd.) Tizanelin Tablet 1 mg (Taisho Pharmaceutical Industries, Ltd.) Tirolbit Tablets 1 mg (Towa Pharmaceutical Co., Ltd.) Tetorinen Tablets 1 mg (Tsuruhara Pharmaceutical Co., Ltd.) Telzanine Tablets 1 mg (Nissin Pharmaceutical Co., Ltd.) Terrelark Tablets 1 mg (Kyowa Pharmaceutical Industry Co., Ltd.) Mekitack Tablets 1 mg (Taiyo Yakuhin Co., Ltd.) Motonalin Tablets 1 mg (Nihon Pharmaceutical Industry Co., Ltd.)

Therapeutic Category	Peripheral nervous system agents-Antispasmodics
Indications	1. Improvement of muscle tightness resulting from the following diseases Cervico-omo-brachial syndrome, lumbago 2. Spastic paralysis resulting from the following diseases Cerebrovascular disorder, spastic spinal paralysis, cervical spondylosis, cerebral (pediatric) palsy, sequelae of trauma (spinal cord injury, head trauma), spinocerebellar degeneration, multiple sclerosis, amyotrophic lateral sclerosis

≪**PRECAUTIONS** (underlined parts are additions)≫

[Contraindications]	Patients with serious hepatic disorder
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatitis, hepatic function disorder, jaundice:** Hepatitis, hepatic function disorder, jaundice with significant elevations of AST(GOT) or ALT(GPT) etc., nausea/vomiting, anorexia, generalized malaise, etc. may occur. Discontinue administration and take appropriate measures in such cases.
<Reference Information>	The number of reported adverse reaction cases in about the last 3 years (April 2004 to October 2007) (events for which a causality to the drug could not be denied) • Hepatitis: 2 cases (no fatal case) The number of patients treated with Tizanidine for a year estimated by MAH: approximately 1.13million (2006) Marketed in Japan in: May 1988 (tablets) July 1994 (granules)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Low back pain, compression fracture of thoracolumbar spine (hyperlipidaemia, hypertension, hepatic steatosis)	3 mg 69 days	**Drug-induced hepatitis** The patient was being monitored as an outpatient at the department of internal medicine for hyperlipidaemia, and was also visiting orthopedic specialist for low back pain. She was receiving a nonsteroidal anti-inflammatory analgesic and limaprost alfadex, as well as intermittent elcatonin injections. On day 1 of administration: Administration of this drug was initiated for low back pain. On day 35 of administration: No particular changes in symptoms were seen. High blood pressure (150/90 mmHg) persisted since the previous month and pulse rate was 112/min. Medication was changed from benidipine hydrochloride to 25 mg/day of atenolol. AST (GOT) 28 IU/L, ALT (GPT) 15 IU/L, γ-GTP 120 IU/L, CK (CPK) 56 IU/L. On day 63 of administration: No changes in symptoms were seen. Blood test during a regular visit showed that AST (GOT) 565 IU/L, ALT (GPT) 447 IU/L, γ-GTP 131 IU/L and LDH 591 IU/L. Evidence of hepatic function disorder was observed (drug-induced hepatitis).

				On day 64 of administration: The patient was hospitalized. Atenolol was discontinued, and administration of glycyrrhizin/glycine/cysteine was initiated. Abdominal echo, abdominal CT and MRCP (magnetic resonance cholangiopancreatography) showed no abnormalities that would provide an explanation for laboratory abnormalities. On day 69 of administration (day of discontinuation): Despite discontinuation of atenolol and administration of glycyrrhizin/glycine/cysteine, AST (GOT) 309 IU/L, ALT (GPT) 335 IU/L and γ-GTP 136 IU/L demonstrated lack of improvements. Since γ-GTP had worsened instead, this event was considered related to this drug rather than atenolol, and administration of this drug was discontinued. 5 days after discontinuation: AST (GOT), ALT (GPT), and γ-GTP began to improve to 140 IU/L, 202 IU/L, and 116 IU/L, respectively. 6 days after discontinuation: DLST results: Positive for this drug 12 days after discontinuation: The patient was discharged.
	Concomitant medications: limaprost alfadex, benidipine hydrochloride, loxoprofen sodium, plaunotol, alendronate sodium hydrate, pravastatin sodium, atenolol, triazolam, elcatonin			

Clinical Laboratory Values

	Approx. 5 months before administration	On day 35 of administration	On day 63 of administration	On day 64 of administration	On day 67 of administration	On day 69 of administration (day of discontinuation)	2 days after discontinuation	5 days after discontinuation	9 days after discontinuation
WBC (/mm^3)	3700	—	5100	4100	3600	3600	3400	3100	3500
Neutrophils (%)	—	—	—	61.8	—	—	54	—	44
Eosinophils (%)	—	—	—	4.9	—	—	9	—	6
Basophils (%)	—	—	—	0.7	—	—	0	—	0
Monocytes (%)	—	—	—	8.9	—	—	10	—	10
Lymphocytes (%)	—	—	—	23.7	—	—	27	—	40
AST (GOT) (IU/L)	41	28	565	534	442	309	284	140	35
ALT (GPT) (IU/L)	21	15	447	430	415	335	300	202	59
γ-GTP (IU/L)	149	120	131	—	124	136	129	116	87
LDH (IU/L)	—	—	591	492	473	—	359	254	202
Total bilirubin (mg/dL)	—	—	0.7	—	0.6	0.6	0.7	0.7	0.6

WBC: White Blood Cell
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
γ-GTP: γ-Glutamyltranspeptidase
LDH: Lactate Dehydrogenase

3 Thiamazole

Brand Name (name of company)	Mercazole tablets 5 mg, Mercazole injection 10 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Hormones-Thyroid and parathyroid hormone preparations
Indications	Hyperthyroidism

<Reason for Revision>

It has been described that agranulocytosis might occur in patients with thiamazole and that "in general, haematological examination including differential leukocyte count should be performed once every 2 weeks for at least 2 months after initiating administration of thiamazole, and periodically thereafter" in the "Important precautions" and "Clinically significant adverse reactions" sections of the package insert as well.
However, the MHLW has received reports of non-compliance of periodic haematological examination, leading to the occurrence of agranulocytosis in some cases. In view of this, the MHLW has called for reminding healthcare professionals of the above alert by revision of the package insert to include the following description in a boxed warning.

≪**PRECAUTIONS** (underlined parts are additions)≫

[Warning]

WARNING

It has been reported that serious angranulocytisis occurred most commonly within 2 months after initiating administration, resulting in death in some cases. As a general, haematological examination including differential leukocyte count should be performed once every 2 weeks for at least 2 months after initiating administration of thiamazole, and periodically thereafter. If abnormalities such as a decreasing tendency in granulocytes are observed, administration should be immediately discontinued and appropriate measures should be taken. Caution should also be exercised when restarting administration once after discontinuation. Before starting therapy with this drug, patients should be advised that adverse reactions such as agranulocytosis may develop, and that periodic haematological examination is necessary. Patients should also be instructed to:

(1) report immediately to their physicians, if symptoms of agranulocytosis (pain pharynx, pyrexia, etc.) occur.
(2) visit their hospitals for periodic haematological examination that should be performed, as a general, once every two weeks for at least 2 months after initiating administration.

[Important Precautions]

Clinically significant adverse reactions such as agranulocytosis may occur most commonly within the first 2 months after initiating the therapy with this product. When starting the therapy with this product, careful consideration should be given to the efficacy and safety. Administration should be limited to patients who are considered appropriate for treatment with this product.

[Adverse Reactions (clinically significant adverse reactions)]

Pancytopaenia, aplastic anaemia, agranulocytosis, white blood cell decreased:
Pancytopaenia, aplastic anaemia, agranulocytosis and white blood cell decreased (initial symptoms: pyrexia, general malaise, pain pharynx, etc.) may occur. Patients should be carefully monitored, and if abnormalities are observed, administration should be immediately discontinued, and appropriate measures should be taken.

<Reference Information>

The number of patients with thiamazole for a year estimated by MAH: approximately 1.3 million (2006)
Marketed in Japan in**:** July 1956 (tablets)
February 1958 (injection)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Hyperthyroidism (thoracic aortic dissection)	5 mg 65 days	**Agranulocytosis** Approx. 8 years before administration: The struma was removed. Approx. 4 months before administration: The patient was hospitalized in Hospital A for thoracic aortic dissection. Administration of 25 μg of levothyroxine sodium was initiated for hypothyroidism after strumectomy. 2 days before administration: The patient was transferred to hospital B for treatment of depression. On day 1 of administration: Since FT_3 increased to 5.3 pg/mL and FT_4 increased to 1.94 ng/dL, administration of 5 mg of this drug (tablets) was initiated. On day 17 of administration: The patient was hospitalized for tests at Hospital C due to suspicion of lung carcinoma (mediastinal part). Biopsy and radiotherapy were both refused. On day 37 of administration: The patient was hospitalized at Hospital B again for treatment of depression. On day 42 of administration: Administration of mianserin Hydrochloride was initiated (1 tablet/day). On day 62 of administration: Pain pharynx and pyrexia developed. On day 65 of administration (day of discontinuation): The patient was emergently hospitalized at Hospital A for dyspnoea. Pneumonia was observed, and agranulocytosis with white blood cell count of 830/mm^3 (neutrophils 0%) was confirmed. No response was seen with steroid pulse therapy. Administration of this drug was discontinued. 7 days after discontinuation: White blood cell count was 28010/mm^3 through use of filgrastim (genetical recombination). 8 days after discontinuation: Although white blood cell count increased to 27200/mm^3, pneumonia was significantly aggravated in X-rays. MRSA was identified in sputum culture. The patient had reached DIC state based on test data. She died.
	Concomitant medications: mianserin hydrochloride, ursodeoxycholic acid, allopurinol, nifedipine, telmisartan, valsartan, amlodipine besilate, etizolam, paroxetine hydrochloride, sulpiride, olanzapine, chlorpromazine/promethazine, nitrazepam, brotizolam, levothyroxine sodium			

Clinical Laboratory Values

	2 days before administration	On day 18 of administration	On day 32 of administration	On day 65 of administration (day of discontinuation)	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation	7 days after discontinuation	8 days after discontinuation
WBC (/mm^3)	4600	—	4650	830	400	660	1280	2800	28010	27200
Neutrophils (%)	—	—	48.0	0	2.5	49.3	—	26.4	46.0	49.0
FT_4 (ng/dL)	1.94	0.49	—	—	—	—	—	—	—	—
FT_3 (pg/mL)	5.3	1.6	—	—	—	—	—	—	—	—
TSH (μU/mL)	<0.10	3.84	—	—	—	—	—	—	—	—

WBC: White Blood Cell
FT_4: Free Thyroxine
FT_3: Free Triiodothyronine
TSH: Thyroid Stimulating Hormone

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 20s	Basedow's disease (epilepsy)	30 mg 25 days ↓ 20 mg 21 days ↓ 15 mg 11 days	**Agranulocytosis** On day 1 of administration: Administration of this drug (tablets) was initiated. White blood cell count 4100/mm^3, neutrophils 49.5%. On day 26 of administration: White blood cell count 2700/mm^3, neutrophils 43.5%. On day 47 of administration: White blood cell count 2300/mm^3, neutrophils 61.0%. On day 56 of administration: Pain pharynx and pyrexia developed. On day 57 of administration: The patient was examined at department of internal medicine for haematology, respiratory medicine and rheumatology. After blood sampling, she went home. White blood cell count 500/mm^3, CRP 12.89 mg/dL. When she was contacted about having agranulocytosis, agreement from her to visit hospital could not be obtained. On day 60 of administration (day of discontinuation): The patient was hospitalized in the same department (clean room). White blood cell count 300/mm^3, neutrophils 0%, CRP 26.27 mg/dL. This drug was discontinued, and treatment through 300 μg/day of G-CSF and antibiotics was initiated. 17 days after discontinuation: Pulse rate 160/minute, blood pressure 70 mmHg. Vasopressor treatment was initiated. APTT was prolonged at 78 seconds. Fresh frozen human plasma was administered. 18 days after discontinuation: White blood cell count 2400/mm^3. Neutrophils finally increased to 42%. DIC markers also increased, administration of low-molecular-weight heparin was initiated. With Cr of 1.5 mg/dL, AST (GOT) of 163 IU/L and LDH of 1075 IU/L, multi-organ failure including hepatic failure, renal failure and cardiac failure developed.

				19 days after discontinuation: The patient was transferred to department of internal medicine for cardiovascular disease, kidneys, internal secretion. She was put on artificial respirator, percutaneous cardiopulmonary portable system. 20 days after discontinuation: Although treatment for cardiac failure was attempted, the patient died.
	Concomitant medications: ebastine, metoprolol tartrate, phenytoin, propranolol hydrochloride			

Clinical Laboratory Values

	On day 1 of administration	On day 26 of administration	On day 47 of administration	On day 57 of administration	On day 60 of administration (day of discontinuation)	8 days after discontinuation	13 days after discontinuation	14 days after discontinuation	18 days after discontinuation	19 days after discontinuation	20 days after discontinuation
WBC (/mm^3)	4100	2700	2300	500	300	700	900	1000	2400	7900	14700
Neutrophils (%)	49.5	43.5	61.0	—	0	0	0	0	42	70	54.5
FT_4 (ng/dL)	7.77	1.27	0.9	—	—	4.26	—	—	—	—	3.61
T_3 (ng/dL)	651.0	185.2	145.9	—	—	360.4	—	—	—	—	211.5
TSH (μIU/mL)	0.014	—	0.013	—	—	0.015	—	—	—	—	0.035

WBC: White Blood Cell
FT_4: Free Thyroxine
T_3: Triiodothyronine
TSH: Thyroid Stimulating Hormone

2

Revision of PRECAUTIONS (No. 192)

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 Notification dated October 31, 2007 (excluding those presented in "1. Important Safety Information" of this Bulletin).

<Reasons for revision of 1 to 8 below>

It has been described that suicidal attempts are inherent in patients with depression and further that sertraline hydrochloride, paroxetine hydrochloride hydrate, fluvoxamine maleate and milnacipran hydrochloride increase suicidal ideation and attempts in patients under age of 18 after administration of antidepressants in the "PRECAUTIONS" section of the package inserts.
Since the results of the short-term placebo-control trials with several antidepressants showed that the risk of suicidal ideation and attempts increased in patients aged 24 and younger, recently the package inserts of antidepressants in the United States have been, as a whole revised. Therefore, the MHLW has called for reminding healthcare professionals of the following alerts by revision of the "PRECAUTIONS" section in the package inserts, as general precautions of antidipressants.

(1) Antidepressants may increase the risk of suicidal ideation and attempts in patients aged 24 and younger.
(2) Patients with symptoms of depression have suicidal ideation, and an increased risk of suicidal attempts.
(3) Families and caregivers should be fully advised of the risks of suicidal ideation and attempts in PRECAUTIONS.

<Psychotropics>

1 Amitriptyline Hydrochloride, Imipramine Hydrochloride, Clomipramine Hydrochloride (oral dosage form), Dosulepin Hydrochloride, Trazodone Hydrochloride, Mianserin Hydrochloride

[Brand Name]

Tryptanol Tablets 10 and 25 (Banyu Pharmaceutical Co., Ltd.) and others
Imidol Sugar-coated Tablets (10) and (25) (Mitsubishi Tanabe Pharma Corporation), Tofranil Tablets 10 mg and 25 mg (Novartis Pharma K.K.)
Anafranil Tablets 10 mg and 25 mg (Alfresa Pharma Corporation)
Prothiaden Tablet 25 (Kaken Pharmaceutical Co., Ltd.)
Desyrel Tablets 25 and 50 (Pfizer Japan Inc.), Reslin Tablets 25 and 50 (Nippon Organon K.K.) and others
Tetramide Tablet 10 mg and 30 mg (Nippon Organon K.K.)

[Precautions of Indications]

Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions]

Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor

restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Other Precautions]

As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants including this drug conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

---

2 <Psychotropics> Amoxapine

[Brand Name]

Amoxan Fine Granules 10%, Amoxan Capsules 10 mg, 25 mg and, 50 mg (Wyeth K.K.)

[Precautions of Indications]

Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions]

Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), acute generalized exanthematous pustulosis: Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome) and acute generalized exanthematous pustulosis may occur. If these symptoms occur, discontinue administration of this drug.

[Other Precautions]

As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

<Psychotropics>

3 Clomipramine Hydrochloride (injectable dosage form)

[Brand Name] Anafranil Injection (Alfresa Pharma Corporation)

[Precautions of Indications] Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions] Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken.

[Other Precautions] As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants including this drug conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

<Psychotropics>

4 Setiptiline Maleate, Trimipramine Maleate, Nortriptyline Hydrochloride, Maprotiline Hydrochloride , Lofepramine Hydrochloride

[Brand Name] Tecipul Tablet (Mochida Pharmaceutical Co., Ltd.) and others
Surmontil Powder 10%, Surmontil Tablets 10 mg and 25 mg (Shionogi & Co., Ltd.)
Noritren Tablet 10 mg and 25 mg (Dainippon Sumitomo Pharma Co., Ltd.)
Ludiomil Tablets 10 mg, 25 mg, and 50 mg (Novartis Pharma K.K.) and others
Amplit Tablets 10 mg and 25 mg (Daiichi-Sankyo Co., Ltd.)

[Precautions of Indications] Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions] Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken.
Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Other Precautions] As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

<Psychotropics>

5 Sertraline Hydrochloride

[Brand Name] Jzoloft Tablets 25 mg and 50 mg (Pfizer Japan Inc.)

[Precautions of Indications] Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions] Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families**,** etc**.** should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Use in Children] "Pooled analyses of overseas short-term (4-16 weeks) placebo-controlled trials of antidepressant drugs including this drug in patients under the age of 18 years with major depressive disorder (MDD) and other psychiatric disorders have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trails. Long-term use has not been evaluated." was omitted.

[Other Precautions] As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants including this drug conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

<Psychotropics>

6 Paroxetine Hydrochloride Hydrate

[Brand Name] Paxil Tablets 10 mg and 20 mg (GlaxoSmithKline K.K.)

[Precautions of Indications] Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance

this risk and benefit in using this drug in such patients.

[Important Precautions]

Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Other psychiatric conditions for which this drug is prescribed can also be at a risk of a suicidal attempt and may be co-morbid with depression and depressive episode. The same precautions should therefore be observed when treating such patients.
Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Use in Children]

"Pooled analyses of overseas short-term (4-16 weeks) placebo-controlled trials of antidepressant drugs including this drug in patients under the age of 18 years with major depressive disorder (MDD) and other psychiatric disorders have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trails. Long-term use has not been evaluated." was omitted.

[Other Precautions]

As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants including this drug conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.
As a result of an analysis of placebo controlled clinical trials of adults with psychiatric disorders conducted overseas, there was a statistically significant increase in the frequency of suicidal attempts in patients with MDD treated with this drug compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]). The majority of these attempts for this drug were in younger adults aged 18-30 years.

---

7 <Psychotropics> Fluvoxamine Maleate

[Brand Name]

Depromel Tablets 25 and 50 (Meiji Seika Kaisha Ltd.), Luvox Tablets 25 and 50 (Solvay Seiyaku K.K.)

[Precautions of Indications]

Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions] Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Use in Children] "Pooled analyses of overseas short-term (4-16 weeks) placebo-controlled trials of antidepressant drugs in patients under the age of 18 years with major depressive disorder (MDD) and other psychiatric disorders have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trails. Long-term use has not been evaluated." was omitted.

[Other Precautions] As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants including this drug conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

---

8 <Psychotropics> Milnacipran Hydrochloride

[Brand Name] Toledomin Tablets 15 and 25 (Asahi Kasei Pharma Corporation)

[Precautions of Indications] Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients aged 24 and younger, prescribers must balance this risk and benefit in using this drug in such patients.

[Important Precautions] Since the possibility of suicidal ideation is inherent in patients with depressive symptoms and such patients have a risk of suicidal attempts, careful monitoring for their conditions and changes in their diseases should be started in an early phase of treatment or at the time of dose changes. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Use in Children] "Pooled analyses of overseas short-term (4-16 weeks) placebo-controlled trials of other antidepressant drugs in patients under the age of 18 years with major depressive disorder (MDD) and other psychiatric disorders have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trails. Long-term use has not been evaluated." was omitted.

[Other Precautions] As a result of an analysis of the short-term placebo-controlled clinical trials with several antidepressants conducted overseas in patients with psychiatric disorders including major depressive disorder (MDD), higher risk of suicidal ideation and attempts was reported in patients aged 24 and younger in the antidepressant group compared to placebo. An increase in the risk of suicidal ideation and attempts with antidepressants was not shown in adults beyond age 24 compared to placebo; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

---

9 <Other hormone preparations> Gemeprost

[Brand Name] Preglandin vaginal suppository (Ono Pharmaceutical Co., Ltd.)

[Contraindications] Patients with a history of hypersensitivity to ingredients of this drug

[Adverse Reactions (clinically significant adverse reactions)] Shock may occur. Patient should be carefully monitored, and if symptoms such as blood pressure decreased and consciousness disturbed are observed, administration should be discontinued and appropriate measures should be taken.

---

10 <Antibiotics> Idarubicin Hydrochloride

[Brand Name] Idamycin injection (Pfizer Japan Inc.)

[Important Precautions] Inoculation of a live or attenuated live vaccine in patients with decreased immune function following administration of this drug may cause vaccine-derived infection enhanced or persisted. Patients should not be inoculated with the vaccines while being treated with this drug.

---

11 <Miscellaneous> Gadopentetate Dimeglumine

[Brand Name] Magnevist, Magnevist syringe (Bayer Yakuhin, Ltd.)

[Relative Contraindications] Patients with serious renal disorder (Nephrogenic systemic fibrosis may occur. The drug is essentially cleared through the kidney. If this product is administered to patients with decreased kidney function, worsening of conditions including renal failure acute etc. may occur due to delayed excretion.)

[Adverse Reactions (clinically significant adverse reactions)] **Nephrogenic systemic fibrosis (NSF):** Nephrogenic systemic fibrosis may occur in patients with serious renal disorders. Patient should be carefully monitored for the emergence of itchiness of the skin, swelling, sclerema, joint stiffness, muscle weakness etc. following administration.

---

12 <IVD (in vitro diagnostics)> Advantage Test Strips S

[Warning]

WARNING

The following patients should not be treated with this product, since overestimation of blood glucose levels may occur. (A false high glucose reading can lead to the administration of a hypoglycaemic agent including insulin, followed by serious symptoms of hypoglycemia such as coma.)

- Patients receiving infusion therapy solutions etc. (note: overestimation of blood glucose levels occurs when a patient is receiving infusions containing maltose.)
- Patients receiving dialysis solution containing icodextrin
- Patients undergoing galactose tolerance test
- Patients undergoing xylose absorption test
- Patients receiving pralidoxime iodide

As a general rule, this product is intended for home use by diabetic patients for glucose monitoring.

[Precautions in Use (interfering substances/drugs)]

Pralidoxime iodide may cause overestimation of blood glucose level.

<Reference Information>

Among blood glucose self-monitoring kits (only those using the enzyme glucose dehydrogenase and coenzyme pyroloquinoline quinone), falsely high glucose results were obtained with this product in a study of glucose determination in the presence of pralidoxime iodide, conducted by the company.

3

List of products subject to Early Post-marketing Phase Vigilance

(As of December 1, 2007)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Pegvisomant (Genetical recombination) / Somavert for s.c. Injection 10 mg, 15 mg, and 20 mg	Pfizer Japan Inc.	June 5, 2007
Salmeterol Xinafoate/Fluticasone Propionate / Adoair 100 Diskus, 250 Diskus, and 500 Diskus	GlaxoSmithKline K.K.	June 8, 2007
Ciclesonide / Alvesco 50 μg Inhaler 112 puffs, 100 μg Inhaler 112 puffs, and 200 μg Inhaler 56 puffs	Teijin Pharma Limited	June 8, 2007
Fondaparinux Sodium / Arixtra Injection 1.5 mg and 2.5 mg	GlaxoSmithKline K.K.	June 8, 2007
Imidafenacin / Uritos Tablets 0.1 mg	Kyorin Pharmaceutical Co., Ltd.	June 11, 2007
Imidafenacin / Staybla Tablets 0.1mg	Ono Pharmaceutical Co., Ltd.	June 11, 2007
Ezetimibe / Zetia Tablets 10 mg	Schering-Plough K.K.	June 11, 2007
Bevacizumab (Genetical recombination) / Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16mL	Chugai Pharmaceutical Co., Ltd.	June 11, 2007
Celecoxib / Celecox Tablets 100 mg and 200 mg	Astellas Pharma Inc.	June 12, 2007
Sodium Risedronate Hydrate / Actonel Tab. 17.5 mg	Ajinomoto Co., Inc.	June 15, 2007
Sodium Risedronate Hydrate / Benet Tablets 17.5 mg	Takeda Pharmaceutical Company Limited	June 15, 2007
Monobasic Sodium Phosphate Monohydrate/Dibasic Sodium Phosphate Anhydrous / Visiclear Tablets	Zeria Pharmaceutical Co., Ltd.	June 15, 2007
Amiodarone Hydrochloride / Ancaron Injection 150	Sanofi-Aventis K.K.	June 22, 2007
Carteolol Hydrochloride / Mikelan LA Ophthalmic Solution 1% and 2%	Otsuka Pharmaceutical Co., Ltd.	July 3, 2007
Darbepoetin Alfa (Genetical recombination) / Nesp Injection Syringe 10 μg syringe, 15 μg syringe, 20 μg syringe, 30 μg syringe, 40 μg syringe, 60 μg syringe, and 120 μg syringe	Kirin Pharma Company, Limited	July 9, 2007
Fludarabine Phosphate / Fludara Tab. 10 mg	Bayer Yakuhin, Ltd.	July 12, 2007
Estradiol / l'estrogel 0.06%	Shiseido Co., Ltd.	August 9, 2007

Tadalafil Cialis Tablets 5 mg, 10 mg, and 20 mg	Eli Lilly Japan K.K.	September 12, 2007
Topiramate Topina Tablets 50 mg and 100 mg	Kyowa Hakko Kogyo Co., Ltd.	September 26, 2007
Montelukast Sodium Kipres Fine Granules 4 mg	Kyorin Pharmaceutical Co., Ltd.	October 2, 2007
Montelukast Sodium Singulair Fine Granules 4 mg	Banyu Pharmaceutical Co., Ltd.	October 2, 2007
Rocuronium Bromide Eslax Intravenous 25 mg/2.5 mL and 50 mg/5.0 mL	Nippon Organon K.K.	October 2, 2007
Garenoxacin Mesilate Hydrate Geninax Tablets 200 mg	Toyama Chemical Co., Ltd.	October 5, 2007
Idursulfase (Genetical recombination) Elaprase Solution for Intravenous Drip 6 mg	Genzyme Japan K.K.	October 17, 2007
Pilocarpine Hydrochloride Salagen Tab. 5 mg*1	Kissei Pharmaceutical Co., Ltd.	October 19, 2007
Nicorandil Sigmart Injection 2 mg, 12 mg, and 48 mg*2	Chugai Pharmaceutical Co., Ltd.	October 19, 2007
Clopidogrel Sulfate Plavix Tablets 25 mg and 75 mg*3	Sanofi-Aventis K.K.	October 19, 2007
Loratadine Claritin Tablets 10 mg, Claritin RediTab Tablets 10 mg*4	Schering-Plough K.K.	October 19, 2007
Travoprost Travatanz Ophthalmic Solution 0.004%	Alcon Japan Ltd.	October 25, 2007
Strontium Chloride (^{89}Sr) Metastron Injectable	Nihon Medi-Physics Co., Ltd.	October 31, 2007
Eplerenone Selara Tablets 25 mg, 50 mg, and 100 mg	Pfizer Japan Inc.	November 13, 2007
Estradiol Divigel 1 mg	Pola Pharma Inc.	November 20, 2007

*1: An additional indication for "the treatment of symptoms of dry mouth in patients with Sjogren's syndrome"

*2: An additional indication for "cardiac failure acute (including acute exacerbation of cardiac failure chronic)"

*3: An additional indication for "acute coronary syndrome (unstable angina pectoris, non ST segment elevation myocardial infarction) to which percutaneous coronary intervention (PCI) is being planned"

*4: Additional administration for "pediatrics"