Pharmaceuticals and Medical Devices Safety Information

No. 220 December 2005

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 also 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
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1

Important Safety Information

This section presents contents of revisions, reference materials 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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 219).

1 Amiodarone Hydrochloride

Brand Name (name of company)	Ancaron Tablets 100 (Aventis Pharma Limited)
Therapeutic Category	Antiarrhythmic agents
Indications	Following cases of life-threatening recurrent arrhythmias that do not respond to or are inappropriate for other available antiarrhythmics Ventricular fibrillation, ventricular tachycardia, and atrial fibrillation with hypertrophic cardiomyopathy

<<**PRECAUTIONS** (underlined parts are additions)>>

[Important Precautions]

Liver: Hepatic enzyme increased may occur. In general, only hepatic enzyme abnormalities may be noted, however, <u>serious</u> liver disorder may occur and fatal cases have been reported.

[Adverse Reactions (clinically significant adverse reactions)]

<u>Hepatitis fulminant,</u> hepatic cirrhosis, liver disorder: <u>Since hepatitis fulminant,</u> hepatic cirrhosis, and liver disorder may occur, and fatal cases have been reported. Patients should be carefully monitored and if abnormalities are observed, take appropriate measures such as discontinuation of administration.

<Reference Information>

Company report
Number of related adverse reaction reports since the initial marketing (approximately 13 years)
(exclusive of "causality could be denied" and inclusive of "causality unknown")
• Hepatitis fulminant: 3 cases (of which 3 had fatal cases)
The number of patients treated with Amiodarone for a year estimated by MAH (Marketing Authorisation Holder): approximately 25000 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Improvement of ventricular tachycardia (mitral valve incompetence, chronic cardiac failure)	400 mg 9 days ↓ 100 mg 3 days	**Hepatitis fulminant** On day 1 of administration: Administration of this drug at 400 mg was started for ventricular tachycardia. On day 5 of administration: The patient experienced queasy in epigastric area since the evening. On day 7 of administration: Mild hepatorenal disorder was confirmed. On day 10 of administration: Dosage of this drug was reduced to 100 mg. Severity of hepatorenal disorder was worsened to moderate. On day 11 of administration: Small amounts of melaena and discomfort in epigastric area through right hypochondrium were confirmed. 1 day after discontinuation: The patient experienced wooziness and was hit with a debilitating feeling of exhaustion in the early morning. Symptoms such as bumping head on the bed and being unable to grip objects were manifested. Liver disorder became severe and infusion therapy of diuretic was started. 2 days after discontinuation: Although blood concentration was as low as 155 ng/mL for amiodarone and 87 ng/mL for desethylamiodarone, gabexate mesilate was used for suspected hepatitis fulminant and disseminated intravascular coagulation syndrome. Also, treatments such as plasma exchange using 40 units of fresh-frozen human plasma were taken. Although conscious levels etc. were transiently improving, the patient died from ventricular tachycardia and ventricular fibrillation. Cause of death: hepatitis fulminant, disseminated intravascular coagulation syndrome	Company report
	Concomitant medications: enalapril maleate, furosemide				

Clinical Laboratory Values

	1 day before administration	On day 3 of administration	On day 7 of administration	On day 10 of administration	1 day after discontinuation	2 days after discontinuation
AST (GOT) (IU/L)	20	19	53	337	1067	2601
ALT (GPT) (IU/L)	18	21	56	356	962	1692
LDH (IU/L)	373	380	523	970	2227	5896
PLT ($\times 10^4/mm^3$)	19.7	21.6	24.4	19.2	14.9	9.5
Total bilirubin (mg/dL)	0.6	0.6	0.8	1.0	3.8	4.1
Prothrombin time (PT) (seconds)	--	--	--	--	26.7	22.6

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Ventricular tachycardia, atrial tachycardia (congestive cardiomyopathy, cardiac failure, atrial flutter, dementia, and asthma)	50-100 mg For approx. 2 years and 5 months	**Hepatitis fulminant** On day 1 of administration: Treatment was started for cardiac failure due to dilated cardiomyopathy. Administration of this drug (50-100 mg) was initiated as deterioration of cardiac function due to atypical atrial tachycardia was confirmed. The course of the conditions was good as sinus rhythm was maintained by this drug. Approx. in year 2 of administration: Hypothyroidism (asymptomatic) was confirmed. Approx. in year 2 and month 4 of administration: Appetite impaired and decreased activity were confirmed. The patient was hospitalized. She was followed up through replacing thyroid hormone and fluid. This drug (100 mg) was continued for atrial tachycardia and atrial flutter to maintain sinus rhythm as much as possible. Approx. in year 2 and month 5 of administration (day of discontinuation): The patient fell languid and presented with elevated hepatic enzyme level and jaundice. Hepatitis fulminant (non-viral) was suspected. 1 day after discontinuation: Conditions were not improved on the next day and accompanied by DIC. 2 days after discontinuation: The patient was transferred to the department of gastroenterology as jaundice was aggravated. 3 days after discontinuation: As decrease in hepatic enzyme level by steroid pulse therapy was confirmed, the condition was evaluated improved. 5 days after discontinuation: The aspiration led conditions aggravated. Although the patient was resuscitated from transient cardiac-respiratory arrest, brain damage was not recovered. 11 days after discontinuation: The patient died. Necropsy confirmed marked hepatic atrophy (necrosis, degeneration). Cause of death: Hepatitis fulminant, aspiration after the onset of hepatitis fulminant followed by cardiac-respiratory arrest.	Company report
	Concomitant medications: furosemide, spironolactone, digoxin, lisinopril, sofalcone, theophylline, diltiazem hydrochloride, warfarin potassium, levothyroxine sodium				

Clinical Laboratory Values

	Approx. on year 2 and month 4 of administration	Approx. on year 2 and month 5 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	4 days after discontinuation
AST (GOT) (IU/L)	65	8572	9563	3228	153
ALT (GPT) (IU/L)	40	5290	5216	3388	2744
Al-P (IU/L)	153	--	--	--	--
LDH (IU/L)	871	17293	15318	5202	2611
γ-GTP (IU/L)	62	--	--	--	--
PLT ($\times 10^4/mm^3$)	17.3	8.9	4.5	3.1	2.7
Ammonia (μg/dL)	--	--	--	56	71

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
PLT: Platelet

2 Carboplatin

Brand Name (name of company)	Carboplatin Injection 1% "Hexal" (Nippon Hexal Corporation) Carbomerck Injection 1% (Merck Hoei Ltd.) Paraplatin Injection, Paraplatin for Injection 150 mg (Bristol Pharmaceuticals Y.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Head and neck carcinoma, small cell cancer, orchioncus, ovarian cancer;, cervical carcinoma, malignant lymphoma, non-small cell lung cancer Concomitant therapy with other antineoplastics for the following malignant tumors Childhood malignant solid tumor (neuroblastoma/retinoblastoma/hepatoblastoma/central nervous system germ cell tumor, recurrent or refractory Ewing tumor family/nephroblastoma)

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic failure, hepatic function disorder, and jaundice: Hepatic failure, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored through periodic testing etc. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Gastrointestinal necrosis, gastrointestinal perforation, haemorrhage of digestive tract, and gastrointestinal ulcer: Gastrointestinal necrosis, gastrointestinal perforation, haemorrhage of digestive tract, and gastrointestinal ulcer may occur. Patients should be carefully monitored, and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Enterocolitis haemorrhagic and pseudomembranous colitis: Enterocolitis haemorrhagic and pseudomembranous colitis may occur. Patients should be carefully monitored, and if severe abdominal pain or diarrhoea etc. are observed, administration should be discontinued and appropriate measures should be taken.

Acute respiratory distress syndrome: Acute respiratory distress syndrome may occur. Patients should be carefully monitored, and if rapidly progressing dyspnoea, hypoxia, chest X-ray abnormal etc. such as bilateral diffuse lung infiltration shadow are observed, administration should be discontinued and appropriate measures should be taken.

Disseminated intravascular coagulation (DIC): DIC may occur. Patients should be carefully monitored, and if blood test confirms abnormalities in platelet count, serum FDP level, or plasma fibrinogen concentration, administration should be discontinued and appropriate measures should be

taken.
Acute pancreatitis: Acute pancreatitis may occur. Patients should be carefully monitored, and if abnormalities are observed in serum amylase or serum lipase, etc, administration should be discontinued.

<Reference Information>

Company report
Number of related adverse reaction reports since July 1995
(exclusive of "causality could be denied" and inclusive of "causality unknown")

- Hepatic failure, hepatic function disorder, and jaundice: 20 cases (of which 5 had fatal cases)
- Gastrointestinal necrosis, gastrointestinal perforation, haemorrhage of digestive tract, and gastrointestinal ulcer: 14 cases (of which 3 had fatal cases)
- Enterocolitis haemorrhagic, and pseudomembranous colitis: 9 cases (no fatal case)
- Acute respiratory distress syndrome: 2 cases (of which 2 had fatal cases)
- Disseminated intravascular coagulation (DIC): 9 cases (of which 5 had fatal cases)
- Acute pancreatitis: 5 cases (no fatal case)

The number of patients treated with Carboplatin for a year estimated by MAH: approximately 100000 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Lung cancer recurrent (metastatic cerebellar tumour)	250 mg 1 day	**Hepatic function abnormal** On day 1 of administration: The patient had been treated for the second time as an outpatient (this drug 250 mg + paclitaxel 130 mg). 3 days after completion: Hyporexia and malaise manifested around this time. 5 days after completion: The patient made an emergency visit for persisting hyporexia and malaise. He was hospitalized for treatment as the result of blood test indicated marked high levels of AST (GOT) 694 IU/L, ALT (GPT) 1400 IU/L, LDH 952 IU/L. 6 days after completion: The patient experienced peripheral coldness and blood pressure was decreased to the range of 80 mmHg in the night time. The results of arterial blood gas analysis and blood test indicated marked hepatic function abnormal from elevated blood lactate level, AST (GOT) 1670 IU/L and ALT (GPT) 2820 IU/L. Administration of steroid, antihepatitis drugs, and vasopressor etc. was started through central vein (CV). Administration of gabexate mesilate was also started. The data were still not improved and renal impairment and progression of DIC were confirmed. The patient was stage IV lung cancer. The general conditions were aggravated in spite of continuous treatment in the ward. 7 days after completion: The patient died at night. Needle biopsy was conducted (hepatic tissue was obtained). Hepatitis virus (−) Cause of death: acute hepatic failure Autopsy: none	Company report
	Concomitant medications: paclitaxel, sodium alginate, haloperidol				

Clinical Laboratory Values

	14 days before administration	5 days after completion	6 days after completion	7 days after completion
RBC ($\times 10^4/mm^3$)	389	383	356	308
Haematocrit (%)	36.9	36.6	34	30.3
MCH (pg)	31.6	31.2	30.7	32
MCHC (pg)	33.4	32.7	32.2	32.5
MCV (fL)	94.7	95.5	95.4	98.3
Haemoglobin (g/dL)	12.3	12	11	9.8
WBC ($/mm^3$)	6400	8200	7700	10300
Segmented cell (%)	--	--	--	72
Stab cell (%)	--	--	--	12
Eosinophils (%)	0.8	--	--	0
Basophils (%)	0.4			0
Lymphocytes (%)	24.6	--	--	13
Monocytes (%)	4.2	--	--	3
PLT ($\times 10^4/mm^3$)	21.7	14.7	9.7	5.4
FDP (μg/mL)			17.4	20.7
Fibrinogen concentration (mg/dL)	--	--	172	104
AST (GOT) (IU/L)	16	694	1670	3790
ALT (GPT) (IU/L)	11	1400	2820	3750
Al-P (IU/L)	269			310
LDH (IU/L)	280	952	2168	6250
γ-GPT (IU/L)	26	--	--	74
Total bilirubin (mg/dL)	--	0.9	0.9	1.9
Serum sodium (mEq/L)	140	135	131	134
Serum potassium (mEq/L)	4.1	5.3	5.1	5.6
Serum chloride (mEq/L)	101	100	98	93
BUN (mg/dL)	10.9	35.1	54.7	55.3
Serum creatinine (mg/dL)	0.79	0.9	1.22	1.56
Diastolic blood pressure (mmHg)		60	range of 80	
Systolic blood pressure (mmHg)	--	110	--	--
CRP (mg/dL)	0.13	4.57	7.99	6.12
Activated partial thromboplastin time (APPT) (sec.)	--	--	40.4	62.6
Total protein (blood serum) (g/dL)	6.3	5.8	5.5	4.7
Cholinesterase (IU/L)	--	--	--	70
Heart rate (times/min.)	--	120	--	--
PT-INR	--	--	2.03	6.30
LAP (IU/L)	--	--	--	98
PT (sec.)			38	11

RBC: Red Blood Cell
MCH: Mean corpuscular haemoglobin
MCH: Mean corpuscular haemoglobin concentration
MCV: Mean corpuscular volume
WBC: White Blood Cell
PLT: Platelet
FDP: Fibrinogen/Fibrin Degradation Products
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
BUN: Blood Urea Nitrogen
CRP: C-Reactive Protein
PT-INR:
Prothrombin Time-International Normalized Ratio
LAP: Leucine Aminopeptidase
PT: Prothrombin Time

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 50s	Ovarian cancer (hypertension, diabetes mellitus, and hypothyroidism)	600-910 mg 4 courses	**Gastrointestinal necrosis** 138 days before administration: Cytoreductive surgery was conducted at another hospital. 111 days before administration: First course of chemotherapy (this drug + paclitaxel 240 mg) was conducted. 90 days before administration: Second course of chemotherapy (this drug + paclitaxel 240 mg) was conducted. 73 days before administration: Blood platelet count was decreased to $2.0 \times 10^4/mm^3$. 62 days before administration: Third course of chemotherapy (this drug + paclitaxel 240 mg) was conducted. Major adverse reaction: numbness, muscle pain, white blood cell (WBC) decreased (44 days before administration: $1400/mm^3$). 28 days before administration: Interval cytoreductive surgery was conducted. Postoperative course was good. Definite diagnosis: no residual tumor, no lymph node metastases, advanced stage Ic (b) On day 1 of administration: Forth course of chemotherapy (this drug + paclitaxel 232 mg) was conducted. 5 days after completion: Incomplete defecation after administration and unresponsive to laxative or enemas. Abdominal pain lower manifested at around midday which gradually intensified, although no abdominal abnormalities were found. 6 days after completion: The patient vomited twice during night time. Pain was mitigated with pentazocine. Although X-ray showed gas build-up in the transverse colon, niveau was not confirmed. Similar findings were confirmed by CT scan. However, the abdominal pain was extended to the upper abdomen and tenderness was markedly confirmed in the upper abdominal region. The pain intensified to such an extent that analgesics were of no relief. As blood pressure decreased (50-80/32-45 mmHg), DOA administration was implemented from the early afternoon. Blood samples were taken as follows: daytime, WBC was $4500/mm^3$, platelet count was $14.0 \times 10^4/mm^3$; at night, WBC was $2300/mm^3$, platelet count was $5.6 \times 10^4/mm^3$; 1 hour later, WBC count was $1100/mm^3$ and progression of DIC was surmised. Another 2 hours later, emergency surgery was conducted (subtotal colectomy, establishment of stoma, and synechiotomy: haemorrhage volume 5480 mL). 7 days after completion: Immediately after the surgery, WBC was $400/mm^3$ and platelet count was $3.2 \times 10^4/mm^3$. Although blood transfusion was continued, bloody drainage was persisted. 8 days after completion:	Company report

				Patient was unable to recover from DIC and haemorrhagic tendency continued (WBC 400/mm^3, platelet count $0.4 \times 10^4/mm^3$). accumulation of pleural effusion was observed. 9 days after completion: Atrial fibrillation manifested. The patient fell into cardiac arrest in spite of defibrillation. Heart rate was restored through resuscitation. As there was increase in pleural effusion, bilateral thoracic drainage was conducted and bloody pleural effusion was suctioned. Elevation in hepatic enzymes surmised to be due to congestive liver disorder was noted. 10 days after completion: Systemic petechiae and oedema manifested. There was urinary retention and acidosis was progressed. 11 days after completion: The patient died (direct cause of death was multiple organ failure from DIC due to intestinal necrosis).	
	Concomitant medications: paclitaxel, omeprazole, mosapride citrate, sucralfate, thiamazole, amlodipine besilate, voglibose, mecobalamin, magnesium oxide, etizolam				

Clinical Laboratory Values

	Before administration	5 days after completion	6 days after completion (day time)	6 days after completion (night time)	7 days after completion	8 days after completion	9 days after completion
RBC ($\times 10^4/mm^3$)	317	214	--	--	402	254	345
Haemoglobin (g/dL)	9.9	9.8	12.7	10.2	12.5	8.0	10.7
WBC ($/mm^3$)	4200	3400	4500	2300	400	400	300
Neutrophils (%)	85.8	74.7	--	--	38.0	20.0	21.0
PLT ($\times 10^4/mm^3$)	32.2	22.6	14.0	5.6	3.2	0.4	0.5
PT (sec.)	--	--	--	--	18.9	15.8	12.7
FDP (μg/mL)	--	--	--	--	10.8	8.5	11.5
Fibrinogen concentration (mg/dL)	--	--	--	--	101	221	263
AST (GOT) (IU/L)	10	11	93	107	112	175	839
ALT (GPT) (IU/L)	9	9	79	87	37	107	412
Al-P (IU/L)	191	168	--	--	122	88	137
LDH (IU/L)	143	160	279	249	224	397	1218
Total bilirubin (mg/dL)	0.40	0.78	0.43	0.28	3.07	2.54	4.08
CRP (mg/dL)	0.42	0.24	8.47	11.88	7.14	14.98	18.66

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
Prothrombin time: PLT
FDP: Fibrinogen/Fibrin Degradation Products
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 60s	Lung cancer, carcinomatous pleurisy (myocardial infarction old, cerebral infarction, and cerebral arterial aneurysm)	358 mg 1 day	**Enterocolitis** On day 1 of administration: This drug at 358 mg and paclitaxel at 83 mg were administered. Anorexia from the evening was noted. 8 days after discontinuation: Diarrhoea occured 10 times/day. Onset of pyrexia of 38.6°C from the night. Brown-colored watery stool was noted. 9 days after discontinuation: WBC and CRP were 3560/mm^3 and 10.5 mg/dL, respectively. Cefpirome sulfate at 1 g × 2/day was initiated. Antibiotics-resistant lactic acid bacteria were orally administered. 13 days after discontinuation: Pyrexia and diarrhoea persisted. WBC and CRP were 4110/mm^3 and 18 mg/dL, respectively. Panipenem/betamipron at 0.5 mg × 2 times/day was changed to 3 days. Hypokalaemia due to diarrhea was observed. Loperamide hydrochloride and L-aspartate potassium were orally administered. No bacteria had been detected in stool, sputum, or blood from 9 days and 10 days after the discontinuation. Oral intake was very little through almost none from 13 days after discontinuation to death. 21 days after discontinuation: Pyrexia and diarrhoea did not improve. WBC and neutrophil were 820/mm^3, 52.2%, respectively. Panipenem/betamipron was readministered. Fosfluconazole at 400 mg was concomitantly used for one day. G-CSF [nartograstim (Genetical recombination) 50 μg] was subcutaneously injected. X-ray photos confirmed bilateral pulmonary infiltrative shadows. SpO_2 was 93% (room air). 24 days after discontinuation: WBC and neutrophil were 710/mm^3 and 64.5%, respectively. Diarrhoea occurred 23 times/day. The stools were brown-colored muddy stool containing blood. The patient was unable to ingest almost any meals. Fluid replacement was insufficient and oral ingestion was impossible, and the patient was followed up. 25 days after discontinuation: Diarrhoea occured 23 times/day. Panipenem/betamipron, and fosfluconazole were discontinued. 26 days after discontinuation: Oxygen at 1 L/min. was started. Diarrhoea occurred 23 times/day. 27 days after discontinuation: SpO_2 was 96% with oxygen at 1 L/min. Diarrhoea occurred 19 times/day. 28 days after discontinuation: SpO_2 became less than 80% and oxygen was given at 3 L/min; SpO_2 94%. Diarrhoea occurred 15 times/day.	Company report

				29 days after discontinuation: Oxygen at 4 L/min. was started, and slight fever in 37°C range was noted. Ingestion was limited to small amount of fluid. Peripheral circulatory failure developed. SpO_2 was 94% and diarrhoea occurred 13 times/day. 30 days after discontinuation: The patient died in the evening [MRSA (+) was identified by the stool culture obtained on day 27 days after discontinuation]. Cause of death: enterocolitis and neutropenia Autopsy: not performed	
	Concomitant medications: paclitaxel, dexamethasone sodium phosphate, ranitidine hydrochloride, diphenhydramine hydrochloride, ondansetron hydrochloride, spironolactone, aspirin, temocapril hydrochloride, torasemide, furosemide, fluvoxamine maleate, pravastatin sodium, nicorandil, metoprolol tartrate, magnesium oxide				

Clinical Laboratory Values

	14 days before administration	6 days after discontinuation	11 days after discontinuation	15 days after discontinuation	17 days after discontinuation	24 days after discontinuation	27 days after discontinuation
Body temperature (°C)	36.2	36.8	38	38.4	38	37.4	37.8
RBC ($\times 10^4/mm^3$)	437	447	346	327	299	315	277
Haemoglobin (g/dL)	13.4	13.7	10.6	9.9	9.2	9.5	8.3
WBC ($/mm^3$)	5000	4730	3510	1880	1190	710	470
Neutrophils (%)	66	77	84	79.5	81	64.5	57
Eosinophils (%)	1.5	2	1	0.5	1	11.5	15
Basophils (%)	1	1	0.5	0.5	0	0	2.5
Lymphocytes (%)	24	18	6.5	13.5	16	13	14
Monocytes (%)	7.5	2	6.5	3	2	8	8.5
PLT ($\times 10^4/mm^3$)	29.5	21.1	13.1	7.3	5	7.3	6
AST (GOT) (IU/L)	36	18	--	11	--	--	--
ALT (GPT) (IU/L)	49	16		8			
LDH (IU/L)	227	--	--	--	--	--	--
γ-GPT (IU/L)	16	--	--	--	--	--	--
Total bilirubin (mg/dL)	0.6	--	--	--	--	--	--
Serum sodium (mEq/L)	139	137		138	138	137	
Serum potassium (mEq/L)	4.8	4.8	--	2.4	2.3	2.9	--
Serum chloride (mEq/L)	102	102	--	99	97	96	--
BUN (mg/dL)	17	23	--	--	--	31	--
Serum creatinine (mg/dL)	0.9	0.9	--	--	--	0.7	--
Creatinine clearance (mL/min)	55	--	--	--	--	--	--
Diastolic blood pressure (mmHg)	66	88	65	60	64	43	58
Systolic blood pressure (mmHg)	120	113	97	110	118	105	94
CRP (mg/dL)	1	1.4	16.9	18.9	--	22.2	--
Arterial oxygen saturation (SpO_2) (%)	97	97	96	96	96	93	96

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
γ-GPT: γ-Glutamyltranspeptidase
BUN: Blood Urea Nitrogen
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Male 60s	Lung cancer (gastrointestinal ulcer haemorrhage, hypertension, and diabetes mellitus)	450 mg 1 day	**Acute respiratory distress syndrome and disseminated intravascular coagulation** 105 days before administration: Pneumectomy of the lower and middle lobe of the right lung was conducted in the patient with lung cancer. On day 1 of administration: Chemotherapy (this drug 450 mg + paclitaxel 100 mg) was conducted. 1 day after discontinuation: Mildly dull felling in the chest was noted. 3 days after discontinuation: Hyporexia was persisted from the night before. Dexamethasone sodium phosphate at 7.6 mg div (until 4 days after discontinuation) was administered. 4 days after discontinuation: Blood sugar control was deteriorated. The patient asserted his good conditions. Pyrexia of 38.5°C developed at night. 5 days after discontinuation: The patient complained of "his stomach being stuck", "not being able to eat meals", and "dry mouth". Chest X-ray photos confirmed infiltrative shadow in the left lung. The treatment was started as nosocomial pneumonia at first. SpO_2 was decreased to 91% in the afternoon. Depressed level of consciousness, then artificial respiration control was performed. The patient fell into warm shock. Pneumonia followed by sepsis was suspected. SIRS and ARD were diagnosed. No clear findings were observed in head CT. Sivelestat sodium hydrate was administered. Polyethyleneglycol treated human normal immunoglobulin and ceftazidime were administered (until 7 days after discontinuation). Methylprednisolone sodium succinate at 1 g was administered (pulse therapy was performed until 7 days after discontinuation). 6 days after discontinuation: WBC was decreased to 900/mm^3. G-CSF was used. Infiltrative shadow in lung field was extended to right lung as well and was aggravated. Platelet count was $8.1 \times 10^4/mm^3$ and diagnosed as DIC based on Matsuda's DIC diagnostic standards. Imipenem/cilastatin sodium, clindamycin phosphate, lyophilized human antithrombin III concentrate (until 8 days after discontinuation), and 40 units of human platelet concentrate (until 7 days after discontinuation) were administered. 7 days after discontinuation: The patient fell into DIC and multi-organ failure. Artificial dialysis (for hyperkalaemia) was implemented. Gabexate mesilate was administered.	Company report

				8 days after discontinuation: Hyperkalaemia followed by wide QRS led to cardiac arrest. Although cardio-pulmonary resuscitation was conducted, heart rate was not restored. Autopsy: not performed Cause of death: pneumonia and acute respiratory distress syndrome	
	Concomitant medications: paclitaxel, nateglinide, propiverine hydrochloride, naftopidil, sennoside, amlodipine besilate, candesartan cilexetil, omeprazole, sodium ferrous citrate, sodium picosulfate, ondansetron, chlorpheniramine maleate, dexamethasone sodium phosphate				

Clinical Laboratory Values

	On day 1 of administration	5 days after discontinuation	6 days after discontinuation		7 days after discontinuation		8 days after discontinuation
Body temperature (°C)	36.0	--	--		--		--
RBC ($\times 10^4$/mm^3)	364	354	321	301	279	281	272
Haemoglobin (g/dL)	10.7	10.3	9.6	8.9	8.2	8.4	7.8
WBC (/mm^3)	9300	8500	900	800	4300	1300	4900
PLT ($\times 10^4$/mm^3)	29.0	21.4	8.1	3.0	1.4	1.3	6.9
PT (sec.)	--	--	--	--	--	--	12.8
FDP (μg/mL)	--	--	--	--	--	--	6.49
Fibrinogen concentration (mg/dL)	--	--	--	--	--	--	793.0
AST (GOT) (IU/L)	16	10	17	--	22	16	--
ALT (GPT) (IU/L)	24	17	16	--	12	13	--
Al-P (IU/L)	209	159			81		
LDH (IU/L)	128	146	115	--	215	170	--
Serum sodium (mEq/L)	137	134	131	--	137	130	--
Serum potassium (mEq/L)	5.0	5.4	5.4	--	4.8	6.7	--
Serum chloride (mEq/L)	101	98	99	--	101	98	--
BUN (mg/dL)	25	40	54	--	50	73	--
Serum creatinine (mg/dL)	1.4	1.4	1.8	--	2.0	2.5	--
CRP (mg/dL)	0.60	0.24	--	--	36.35	--	--

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
PT: Prothrombin time
FDP: Fibrinogen/Fibrin Degradation Products
ALT: Alanine Aminotransferase
AST: Asparate Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
CRP: C-Reactive Protein

3 Sevoflurane

Brand Name (name of company)	Sevofrane (Maruishi Pharmaceutical Co., Ltd.)
Therapeutic Category	General anesthetics
Indications	General anesthesia

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]

Rhabdomyolysis: Serious renal disorders such as acute renal failure associated with rhabdomyolysis characterized by myalgia, feelings of weakness, CK (CPK) increased and myoglobin blood increased and urine myoglobin increased may occur. If abnormalities are observed, appropriate measures should be taken.
Hepatic function disorder, jaundice: Hepatic function disorder with a a

significant increase in AST (GOT), ALT (GPT) etc. and jaundice may occur. If abnormalities are observed, appropriate measures should be taken.
Serious arrhythmia: Cardiac arrest, atrioventricular block complete, severe severe bradycardia, ventricular extrasystoles, ventricular tachycardia (including torsades de pointes), and ventricular fibrillation may occur. If abnormalities are observed, appropriate measures such as dosage reduction or discontinuation, defibrillation, and cardiopulmonary resuscitation.

<Reference Information>

Number of related adverse reaction reports since the initial marketing (approximately 15 years)
(exclusive of "causality could be denied" and inclusive of "causality unknown")
- Rhabdomyolysis: 5 cases (no fatal case)
- Hepatic function disorder, jaundice: 38 cases (of which 4 had fatal cases)
- Serious arrhythmia: 21 cases (no fatal case)

The number of patients treated with Sevoflurane for a year estimated by MAH: approximately 820000 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 40s	Left jaw cyst, impacted wisdom tooth, periapical periodontitis (hepatic steatosis)	1.2%-5 % 1 day	**Rhabdomyolysis, hyper myoglobinaemia, and acute renal failure** On day 1 of administration: Surgery was conducted for left jaw cyst, impacted wisdom tooth, and periapical periodontitis. Atropine sulfate, hydroxyzine hydrochloride, and roxatidine acetate hydrochloride were administered as preanesthetic medication. Propofol, nitrous oxide, suxamethonium chloride, and this drug were implemented as anesthetic and nitrous oxide, this drug, and buprenorphine hydrochloride were used for maintenance of anesthesia. Anesthetic time was 3 hours and 16 minutes, operation time was 2 hours and 53 minutes. Haematuria was observed immediately after the surgery. 1 day after completion: AST (GOT), ALT (GPT), and LDH were 506 IU/L, 125 IU/L, and 3992 IU/L, respectively. 3 days after completion: Electrolyte fluid at 1000 mL/day and furosemide at 1/2 ampule were administered by IV continuous injection as AST (GOT) 696 IU/L, ALT (GPT) 235 IU/L, LDH 3019 IU/L, and creatinine 2.2 mg/dL were confirmed. 4 days after completion: Electrolyte fluid and furosemide were continuously administered as AST (GOT) 460 IU/L, ALT (GPT) 241 IU/L, LDH 10651 IU/L, and creatinine 2.2 mg/dL were confirmed. Cardiac hypertrophy and pleural effusion were observed in X-ray. 5 days after completion: Electrolyte fluid and furosemide were continuously administered as AST (GOT) 243 IU/L, ALT (GPT) 220 IU/L, LDH 558 IU/L, creatinine 2.5 mg/dL, and CK (CPK) 11290 IU/L were confirmed. Also, artificial dialysis was initiated.	Company report
	Concomitant medications: nitrous oxide, suxamethonium chloride, atropine sulfate, hydroxyzine hydrochloride, roxatidine acetate hydrochloride, propofol, buprenorphine hydrochloride, ephedrine hydrochloride, fosfomycin sodium, flurbiprofen axetil, carbazochrome sodium sulfonate, tranexamic acid				

Clinical Laboratory Values

	Before administration	1 day after completion	3 days after completion	4 days after completion	5 days after completion	6 days after completion	7 days after completion	10 days after completion	14 days after completion
AST (GOT) (IU/L)	26	506	696	460	243	100	54	25	22
ALT (GPT) (IU/L)	61	125	235	241	220	170	159	91	54
LDH (IU/L)	212	3992	3019	1065	558	366	422	365	347
CK (CKP) (IU/L)	98	--	--	35440	11290	3871	1629	413	138
Creatinine (mg/dL)	0.7	1.5	2.2	2.2	2.5	1.8	2.0	2.0	2.2
BUN (mg/dL)	12	26	36	36	39	24	28	27	27

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
CK: Creatine Kinase
BUN: Blood Urea Nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	1st time: abdominal aortic obstruction (none) 2nd time: inferior mesenteric arterial occlusion (none)	1st time: 1.5%-3% 1 day ↓ 2nd time: 1.5%-2% 1 day	**Hepatic function disorder** 1st surgery: Intramuscular injection of atropine sulfate 0.5 mg and hydroxyzine hydrochloride 50 mg were conducted as preanesthetic medication. Intubation for anesthesia induction was implemented with thiopental sodium 300 mg and suxamethonium chloride 60 mg and maintained by 50% of nitrous oxide, 50% of oxygen, and 1.5%-3% of this drug. Vital signs were as stable as heart rate 60-100 beats/min. and 100-150/50-80 mmHg during surgery. Upon returning to the room, flomoxef sodium 4 g/day was administered through IV drip for the prevention of surgical site infection. 2nd surgery: As intense abdominal pain accompanied by muscular guarding occurred 2 days after the previous surgery, emergency surgery was conducted for suspected inferior mesenteric arterial occlusion. Intubation for anesthesia induction was implemented with thiopental sodium 150 mg and vecuronium bromide 7 mg, and maintained by 50% of nitrous oxide, 50% of oxygen, and 1.5%-2% of this drug. 1 day after completion: Body temperature was increased to 37.7°C and improvement of values for liver function test (AST (GOT) 64 IU/L, ALT (GPT) 58 IU/L) were observed. 2 days after completion: Body temperature was increased to 38.0°C with AST (GOT) 4242 IU/L and ALT (GPT) 3699 IU/L. 20 days after completion: Improvements were confirmed with AST (GOT) 17 IU/L, ALT (GPT) 30 IU/L. DLST: this drug (+), flomoxef sodium (+)	Company report
	Concomitant medications: atropine sulfate, hydroxyzine hydrochloride, sodium thiopental, nitrous oxide, vecuronium bromide, flomoxef sodium				

Clinical Laboratory Values

	Before administration	After the 2nd surgery	2 days after completion	9 days after completion	20 days after completion
AST (GOT) (IU/L)	13	41	4242	33	17
ALT (GPT) (IU/L)	13	17	3699	362	30
Al-P (IU/L)	65	61	47	83	95
LDH (IU/L)	140	349	1381	276	236
Total bilirubin (mg/dL)	0.5	0.9	0.5	1.1	0.7

AST: Asparate Aminotransferase ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase LDH: Lactate Dehydrogenase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 10s	Chronic renal failure (Pierre-Robin Syndrome, malformations multiple, and incomplete right bundle branch block)	3 % 1 day	**Atrioventricular block complete** Medical history: ventricular septal defect and atrioventricular block complete On day 1 of administration: CAPD catheterization was conducted for chronic renal failure. No electrocardiogram abnormal was observed at preoperative test. Anesthesia induction was implemented with 60% of oxygen, 40% of nitrous oxide, and 3% of this drug. Blood pressure was decreased to 115/60 mmHg from 180/100 mmHg 5 minutes after the inhalation of this drug. Atrioventricular block complete was observed in electrocardiogram and heart rate became bradycardia of 40 beats/min from 80 beats/min. Although drip infusion was immediately started and total volume of 0.2 mg of atropine sulfate and 4 mg of ephedrine hydrochloride were intravenously administered, the conditions did not improve. After discontinuation of this drug and implementation of intratracheal intubation with 100% oxygen and 1.5 mg of vecuronium bromide, sinus rhythm returned to normal.	Company report
	Concomitant medications: nitrous oxide				

4 Whole Human Blood, Blood for Exchange Transfusion, Fresh-Frozen Human Plasma, Concentrated Human Blood Platelet, Concentrated Human Red Blood Cell, Concentrated Frozen-Thawed Human Red Blood Cells, Washed Human Red Blood Cells, Leukocyte Poor Red Blood Cells

Brand Name (name of company)	**Whole Human Blood** Whole Blood CPD "Nisseki" (Japanese Red Cross Society) Irradiated Whole Blood CPD "Nisseki" (Japanese Red Cross Society) **Blood for Exchange Transfusion** Blood for Exchange Transfusion "Nisseki" (Japanese Red Cross Society) Irradiated Blood for Exchange Transfusion "Nisseki" (Japanese Red Cross Society) **Fresh-Frozen Human Plasma** Fresh Frozen Plasma "Nisseki" (Japanese Red Cross Society) **Concentrated Human Blood Platelet** Platelet Concentrate "Nisseki" (Japanese Red Cross Society) Irradiated Platelet Concentrate "Nisseki" (Japanese Red Cross Society) Platelet Concentrate HLA "Nisseki" (Japanese Red Cross Society) Irradiated Platelet Concentrate HLA "Nisseki" (Japanese Red Cross Society) **Concentrated Human Red Blood Cell** Red Cells M·A·P "Nisseki" (Japanese Red Cross Society)

	Irradiated Red Cells M·A·P "Nisseki" (Japanese Red Cross Society) **Concentrated Frozen-Thawed Human Red Blood Cells** Frozen Thawed Human Red Blood Cells "Nisseki" (Japanese Red Cross Society) Irradiated Frozen Thawed Red Cells "Nisseki" (Japanese Red Cross Society) **Washed Human Red Blood Cells** Washed Red Cells "Nisseki" (Japanese Red Cross Society) Irradiated Washed Red Cells "Nisseki" (Japanese Red Cross Society) **Leukocyte Poor Red Blood Cells** Leukocyte Poor Red Cells "Nisseki" (Japanese Red Cross Society) Irradiated Leukocyte Poor Red Cells "Nisseki" (Japanese Red Cross Society)
Therapeutic Category	Human blood preparations
Indications	**Whole Human Blood** Used to meet the indications of general blood transfusion. **Blood for Exchange Transfusion** Used for ABO blood type incompatibility hemolytic disease of the newborn **Fresh-Frozen Human Plasma** Replenishment of blood coagulation factor. (1) Patients with complex coagulopathy who has haemorrhage or haemorrhage tendency, or preoperative patients. (2) At the time of haemorrhage due to reduced blood coagulation factor or deficiency and specific coagulant or blood coagulant factor is not identified. **Concentrated Human Blood Platelet** (Platelet Concentrate "Nisseki", irradiated Platelet Concentrate "Nisseki") Indicated for diseases accompanying thrombocytopenia. (Platelet Concentrate HLA "Nisseki", Irradiated Platelet Concentrate HLA "Nisseki") Indicated for diseases accompanying thrombocytopenia and the cases ineffective with general platelet preparations due to HLA antigen. **Concentrated Human Red Blood Cell** Indicated for deficiency of red blood cell in the blood or hematoablative conditioning. **Concentrated Frozen-Thawed Human Red Blood Cells** Used for anaemia or depressed red blood cell function. **Washed Human Red Blood Cells** Used for blood transfusion for anaemia or for prevention of adverse reactions due to plasma constituent. **Leukocyte Poor Red Blood Cells** Used for blood transfusion of patients who may develop febrile adverse reactions due to antileukocyte antibody with whole human blood, etc. Used for prevention of producing antileukocyte antibody at the time of blood transfusion for organ transplant.

<<**PRECAUTIONS** (underlined parts are additions)>>

[Warning]	**WARNING** Caution should be exercised for the following items upon blood transfusion therapy. 1) These drugs should be used under doctors sufficiently educated and experienced in blood transfusion. 2) Emergency measures for adverse reactions should be prepared in advance when conducting blood transfusion.
[Important Precautions]	These products comply with virus detecting tests such as for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV-1 and HIV-2) etc. However, risks for infection should be considered as the blood donor may have been in window period etc. If infection is suspected, tests for hepatitis marker or HIV antibody etc. should be performed before and after the blood transfusion and follow-up should be conducted.
[Adverse Reactions (clinically significant adverse reactions and infectious diseases)]	**Respiratory disorder and transfusion-related acute lung injury (TRALI):** Wheezing, hypoxemia, cyanosis, pulmonary oedema, TRALI etc. may occur during or after the blood transfusion. In particular, TRALI is a respiratory disorder accompanying rapid pulmonary oedema, hypoxemia, tachycardia,

hypotension, cyanosis, and dyspnoea, occurs during or within 6 hours after blood transfusion, occasionally resulting in death. If these symptoms manifest, immediately discontinue blood transfusion and take appropriate measures such as administration of oxygen and respiratory control etc.
Cardiac function disturbance/arrhythmia: Serious cardiac function disturbance such as cardiac failure, myocardial disorder, and atrial/ventricular fibrillation etc. and arrhythmia may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures such as discontinuation of blood transfusion should be taken.
Renal impairment: Serious renal impairment such as acute renal failure, etc. may occur. Patients should be carefully monitored, and if abnormalities are observed, appropriate measures should be taken.
Hepatic function disorder: Hepatic function disorder with a significant increase in AST and ALT may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

<Reference Information>

Company report
Number of related adverse reaction reports since the initial marketing (approximately 50 years)
(exclusive of "causality could be denied" and inclusive of "causality unknown")
- Respiratory disorder etc.: 12 cases (of which 9 had fatal cases)
- Cardiac function disturbance/arrhythmia: 9 cases (no fatal case)
- Renal impairment etc.: 5 cases (of which 3 had fatal cases)
- Hepatic function disorder etc.: 7 cases (of which 1 had a fatal case)

The number of patients treated with these drugs for a year estimated by MAH: approximately 1010000 (2003)

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Anaemia postoperative (hypertension, hyperlipidaemia)	4 units 1 time	**Acute respiratory failure** Day of blood transfusion: Pretransfusion conditions: body temperature 37.4°C, blood pressure 93/48 mmHg, pulse rate 105/min. Anaemia of RBC 231 × 10^4/mm^3, haemoglobin 6.9 g/dL, and haematocrit 21% was confirmed. Breath sounds through lower lung field was well auscultated, moist rale was (–) and SpO_2 was around 95% (O_2 mask at 5 L). Permeability loss and atelectasis (–) in both lung fields were confirmed in chest X-ray test. Blood transfusion of 4 units of concentrated human red blood cell was initiated. 4 hours and 20 minutes after initiation of blood transfusion: Blood transfusion was completed. 8 hours and 20 minutes after initiation of blood transfusion: Suddenly productive cough manifested. SpO_2 77% (O_2 mask at 5 L) and pulse rate 130-140/min. Marked moist rale in both lung fields were confirmed in the auscultation of the chest. O_2 mask was switched to Inspiron mask. Respiratory status was rapidly worsened. 8 hours and 40 minutes after initiation of blood transfusion: The patient went cardiac-respiratory arrest. Although cardiopulmonary resuscitation was immediately started, heart rate was not restored.	Company report
				11 hours 10 minutes after initiation of blood transfusion: The patient died due to respiratory failure and cardiac-respiratory arrest.	

	Concomitant medications: dopamine hydrochloride, ulinastatin, roxatidine acetate hydrochloride, cefmetazole sodium, human plasma protein fraction

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Thrombocytopenia (multi-organ failure and pneumocystis carinii pneumonia)	20 units Once	**Atrial fibrillation and blood pressure decreased** Primary disease: mycosis fungoides Pneumocystis carinii pneumonia due to immunodeficient status occurred and became severe with platelets decreased. Before blood transfusion: Blood pressure was maintained in the range of 80 mmHg with catecholamine drug at 10γ. Day of blood transfusion: Blood transfusion of 20 units of human platelet concentrate were initiated with platelet count of $0.6 \times 10^4/mm^3$. 10 minutes after initiation of blood transfusion: Sudden atrial fibrillation, blood pressure decreased, and heart rate decreased (range of 30 beats/min.) occurred. Blood transfusion was discontinued. 15 minutes after initiation of blood transfusion: Circulatory dynamics recovered.	Company report
	Concomitant medications: methylprednisolone sodium succinate, pentamidine isetionate, micafungin sodium, meropenem trihydrate, sivelestat sodium hydrate				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 70s	Preoperative anaemia (none)	4 units Once	**Blood pressure decreased, acute renal failure, and urticaria** Primary disease: rectal cancer and state of intestinal obstruction Day of blood transfusion: Blood pressure was 120 mmHg. Blood transfusion of 4 units of concentrated human red blood cell was initiated. 15 minutes after initiation of blood transfusion: Blood pressure decreased to 94/60 mmHg. 1 hours and 15 minutes after initiation of blood transfusion: Administration of oxygen was initiated. 1 hours and 50 minutes after initiation of blood transfusion: Administration of catecholamine drug was initiated. 4 hours and 45 minutes after initiation of blood transfusion: Human plasma protein fraction was transfused. 5 hours and 30 minutes after initiation of blood transfusion: Diuretic was administered. (no micturition)	Company report

				6 hours and 15 minutes after initiation of blood transfusion: Gabexate mesilate was administered. 8 hours and 55 minutes after initiation of blood transfusion: The patient died. Note) Blood transfusion was not discontinued and total volume was transfused.	
	Concomitant medications: none				

Clinical Laboratory Values

	Pre-transfusion	Post-transfusion
BUN (mg/dL)	22	34
Creatinine (mg/dL)	0.9	1.0
RBC ($\times 10^4/mm^3$)	404	507
Haemoglobin (g/dL)	9.0	12.1
Haematocrit (%)	30.1	38.2
PLT ($\times 10^4/mm^3$)	32.8	18.2

BUN: Blood Urea Nitrogen RBC: Red Blood Cell
PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 70s	Anaemia (hypertrophic cardiomyopathy)	4 units 1 time	**Hepatitis fulminant** The patient was hospitalized for subarachnoid haemorrhage and intra-cerebral haemorrhage. Day of blood transfusion: Percutaneous transluminal cerebral artery angioplasty was conducted. Blood transfusion of concentrated human red blood cell was initiated. 7 days after blood transfusion: Consciousness disturbed manifested. Elevated hepatic deviation enzyme level was observed. AST (GOT) 1436 IU/L, ALT (GPT) 681 IU/L, LDH 4547 IU/L, and prothrombin time prolonged were confirmed. The patient was diagnosed with hepatitis fulminant. Plasma exchange therapy was conducted using 40 units of fresh-frozen human plasma. 8 days after blood transfusion: Although vasopressor was used from before noon, blood pressure was gradually decreased. Plasma exchange therapy was terminated. Ventricular tachycardia manifested at night. Death was confirmed.	Company report
	Concomitant medications: famotidine, nicardipine hydrochloride, haloperidol, phenobarbital, nizofenone fumarate, cefazolin sodium				

Clinical Laboratory Values

	Day of blood transfusion	7 days after blood transfusion (morning)	7 days after blood transfusion (evening)	8 days after blood transfusion
AST (GOT) (IU/L)	78	1436	3784	12426
ALT (GPT) (IU/L)	49	681	1443	1716
LDH (IU/L)	1079	4547	10296	23922
CRP (mg/dL)	0.5	20.7	16.9	7.0
HBsAg	(–)	(–)	(–)	--
HCV-Ab	(+)	--	--	--

AST: Asparate Aminotransferase LDH: Lactate Dehydrogenase
ALT: Alanine Aminotransferase HbsAg: Hepatitis Virus Bs Antigen
Al-P: Alkaline Phosphatase HCV-Ab: Hepatitis C Virus Antibody

5 Phenytoin, Phenytoin Sodium, Phenytoin/Phenobarbital, Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate

● Phenytoin, Phenytoin Sodium

Brand Name (name of company)	Aleviatin Powder 10%, Aleviatin Tablets 25 mg, and 100 mg, Aleviatin Injection 250 mg (Dainippon Sumitomo Pharma Co., Ltd.) Hydantol Power 10%, Hydantol Tablets 25 mg, and 100 mg (Fujinaga Pharm Co., Ltd.) Phenytoin Powder 10% "Kyowa Iryo" (Kyowa Iryo Kaihatsu Co., Ltd.)
Therapeutic Category	Antiepileptics
Indications	(oral dosage form) ○ Convulsive seizures of epilepsy Tonic-clonic seizures (generalized convulsive seizures and grand mal) and focal convulsion (including Jacksonian seizure) ○ Autonomic seizure ○ Psychomotor seizures (injectable dosage form) ○ Prolonged epileptiform convulsive seizures (status epilepticus) ○ Oral administration is impossible and convulsive seizure is highly suspected (especially, consciousness disturbed, preoperative, and postoperative) ○ Immediate control of epileptiform convulsive seizures is required

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]	**Hepatitis fulminant, hepatic function disorder, and jaundice:** Hepatitis fulminant, serious hepatic function disorder with marked elevations of AST (GOT), ALT (GPT) and γ-GTP etc. and jaundice may occur. Patients should be carefully monitored. If abnormalities are observed, appropriate measures such as discontinuation of administration should be taken. **Cerebellar atrophy:** Cerebellar atrophy may occur in cases of long-term administration of phenytoin, and causality with prolonged increase in blood concentration of phenytoin has been suggested. Caution should be exercised for cerebellar symptoms (nystagmus, dyslalia, and ataxia etc.). Patients should be carefully monitored through periodic testing etc. If abnormalities are observed, appropriate measures such as immediate dosage reduction and discontinuation of administration should be taken.

● Phenytoin/Phenobarbital, Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate

Brand Name (name of company)	Aleviatin with Phenobarbital (Dainippon Sumitomo Pharma Co., Ltd.) Hydantol D, Hydantol E, Hydantol F (Fujinaga Pharm Co., Ltd.)
Therapeutic Category	Antiepileptics
Indications	○ Convulsive seizures of epilepsy Tonic-clonic seizures (generalized convulsive seizures and grand mal) and focal convulsion (including Jacksonian seizure) ○ Autonomic seizure ○ Psychomotor seizures

<<**PRECAUTIONS** (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]	**Hepatitis fulminant, hepatic function disorder, and jaundice:** Hepatitis fulminant, serious hepatic function disorder with marked elevations of AST (GOT), ALT (GPT) and γ-GTP etc. and jaundice may occur. Patient should be carefully monitored. If abnormalities are observed, appropriate measures such as discontinuation of administration should be taken. **Cerebellar atrophy:** Cerebellar atrophy may occur in cases of long-term administration, and causality with prolonged increase in blood concentration of this drug has been suggested. Caution should be exercised for cerebellar

symptoms (nystagmus, dyslalia, and ataxia etc.). Patients should be carefully monitored through periodic testing etc. If abnormalities are observed, appropriate measures such as immediate dosage reduction and discontinuation of administration should be taken.

<Reference Information>

Company report
Tsuyoshi Yasunaga, et al.: The Journal of Tohoku district of the Japanese Society of Internal Medicine 2003; 15 (2): 33 (In Japanese)
Masaki Hayakawa, et al.: Psychiatry and Clinical Neuroscience 2000: 42 (11): 1175-1180 (In Japanese)
Hirofumi Goto et al.: Neurology 1995; 43: 355-357 (In Japanese)
Number of related adverse reaction reports since the initial marketing (approximately 65 years)
(exclusive of "causality could be denied" and inclusive of "causality unknown")
- Hepatitis fulminant: 4 cases (of which 2 had fatal cases)
- Cerebellar atrophy: 11 cases (no fatal case)

The number of patients treated with these drugs for a year estimated by the relevant companies: approximately 250000 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 30s	Sequelae of brain contusion (none)	200 mg 402 days ↓ 250 mg 1 day	**Fulminant liver disorder** Medical history: none On day 1 of administration: Phenytoin at 200 mg/day had been administered for symptomatic epilepsy associated with head trauma from a traffic accident. On day 403 of administration (day of discontinuation): The patient failed to wake up in the morning and exhibited hyperthermia, and was transported by ambulance. Conscious level was JCS100 with pyrexia of 39°C to 40°C. Right sided paralysis was observed at the time of hospitalization. Blood concentration of phenytoin was as low as 6.8 μg/mL. Phenobarbital and phenytoin at 100 mg and 250 mg were administered, respectively. No significant abnormal findings in head CT or MRI. Meningitis was denied from lumbar puncture findings. As hepatic function disorder with AST (GOT) 617 IU/L and ALT (GPT) 630 IU/L was confirmed in the blood test conducted at the time of hospitalization, subsequent administration of phenytoin was discontinued. 1 day after discontinuation: Hepatic function disorder was aggravated with AST (GOT) 901 IU/L and ALT (GPT) 1448 IU/L. Platelet count was decreased to 5.7 ×s $10^4/mm^3$. Various types of virus tests indicated negative and autoimmune hepatitis was unlikely as well. Aggravation of brain oedema was confirmed in head CT. Liver supporting therapy used by concentrated glycerin/fructose, glucagons, and insulin was conducted. Although NH_3 remained within normal range, the patient was diagnosed with coma hepatic. Administration of drip infusion of branched chain amino acid was started.	Company report

				2 days after discontinuation: Hepatic function disorder was further aggravated to AST (GOT) 7750 IU/L and ALT (GPT) 10420 IU/L. Total bilirubin was 3.6 mg/dL and jaundice was confirmed. Hepatic functional reserve was markedly decreased to prothrombin time 34.1 sec. and hepaplastin test <8%. FDP was increased to 40 μg/mL. As platelet was further decreased to 3.6 × 10^4/mm^3, the patient was diagnosed with fulminant liver disorder and DIC based on consciousness disturbed and brain oedema etc. Platelet transfusion, steroid pulse therapy, and plasma exchange therapy were conducted. Consciousness level recovered to JCS30 immediately after the implementation of plasma exchange. 3 days after discontinuation: Improving trend in AST (GOT) 2095 IU/L and ALT (GPT) 3065 IU/L were observed. 5 days after discontinuation: Hepatic functional reserve markedly recovered to prothrombin time 15.5 sec. and hepaplastin test 31%. Plasma exchange was conducted only once. 25 days after discontinuation: The result of DLST was (±). 1.5 months after discontinuation: Hepatic function was normalized and hepatic functional reserve was improved to prothrombin time 10.6 sec. and hepaplastin test 125%. Brain oedema nearly disappeared and consciousness became lucid.	
	Concomitant medications: none				

Clinical Laboratory Values

	On day 403 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	5 days after discontinuation	25 days after discontinuation	47 days after discontinuation
RBC (×10^4/mm^3)	548	--	512	--	403	--	--
WBC (/mm^3)	19700	--	12210	--	8600	--	--
PLT (×10^4/mm^3)		5.7	3.6				
AST (GOT) (IU/L)	617	901	7750	2095	341	55	35
ALT (GPT) (IU/L)	630	1448	10420	3065	2252	44	23
Al-P (IU/L)	237	203	206	182	186	180	143
Total bilirubin (mg/dL)	0.5		3.6		4.7		
Direct bilirubin (mg/dL)	--	--	2.6	--	3.1	--	--
γ-GPT (IU/L)	191	260	206	65	138	113	47
LDH (IU/L)	1443	1140	11500	1254	521	386	314
Albumin (g/dL)	5.3	--	--	3.3	--	--	--

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
γ-GPT (IU/L): γ-Glutamyltranspeptidase
LDH: Lactate Dehydrogenase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 70s	Epilepsy, prostatic hyperplasia, and insomnia (none)	300 mg approx. 50 years ↓ 400 mg 18 days	**Cerebellar atrophy and phenytoin intoxication (Stagger in walking, queasy, and vomiting)** Medical history: cancer of sigmoid colon (postoperative) and left renal carcinoma (postoperative) On day 1 of administration: Convulsive seizure occurred. Phenytoin at 300 mg/day was started with the diagnosis of epilepsy. Approx. year 50 of administration (dose escalation day): Dosage of phenytoin was increased to 400 mg/day from 300 mg/day. Approx. year 50 of administration, on day 16 of dose escalation: Gait disturbance (Stagger), queasy, and vomiting occurred around evening and the patient received consultation from a nearby physician. Approx. year 50 of administration, on day 18 of dose escalation (day of discontinuation): The patient was hospitalized to receive close examination and treatment for suspected phenytoin intoxication. Phenytoin intoxication was suspected and ataxic gait, nystagmus, and flapping tremor were observed. Oral administration of phenytoin was discontinued and washout was initiated with fluid replacement and IV injection of diuretic. Cerebellar atrophy was confirmed in CT test on admission. 1 day after discontinuation: Blood concentration of phenytoin was 53.6 μg/mL. Although queasy disappeared with drip infusion in hospital, ataxic gait persisted. 7 days after discontinuation: Cerebellar atrophy was confirmed in head MRI test. 11 days after discontinuation: Blood concentration of phenytoin decreased to 3.0 μg/mL or less. 18 days after discontinuation: Although ataxic gait improved considerably, it still mildly-persisted. The diseases that might cause cerebellar atrophy (alcohol, vitamin deficiency, thyroid disorder, malignant tumor, and spinocerebellar degeneration) were examined for, but the results were negative. Therefore, the patient was diagnosed with cerebellar atrophy due to long-term oral administration of phenytoin.	Article report
	Concomitant medications: chlormadinone acetate, naftopidil, propiverine hydrochloride, brotizolam, zolpidem tartrate				

2

Revision of PRECAUTIONS

(No. 171)

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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 219), together with reference materials (excluding those presented in "1. Important Safety Information" of this Bulletin).

<Hypnotics and sedatives, anxiolytics>

1 Zopiclone

[Brand Name] Amoban Tablets 7.5 and 10 (Aventis Pharma Limited) and others

[Adverse Reactions (clinically significant adverse reactions)] **Anaphylactoid symptoms:** Anaphylactoid symptoms may occur. Patients should be carefully monitored, and if abnormalities such as urticaria and angioedema are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Psychotropics>

2 Chlorpromazine Hydrochloride, Chlorpromazine Hibenzate, Chlorpromazine Phenolphthalinate

[Brand Name] Wintermin Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (Shionogi & Co., Ltd.)
Contomin Sugar-coated Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg, Contomin Intramuscular Injection 10 mg, 25 mg, and 50 mg (Mitsubishi Pharma Corporation), and others
Contomin Powder 10%, Contomin Granules 10% (Mitsubishi Pharma Corporation)
Wintermin Fine Granules (10%) (Shionogi & Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Aplastic anemia, haemolytic anaemia, and agranulocytosis:** Aplastic anemia, haemolytic anaemia, and agranulocytosis may occur. Patients should be carefully monitored, and if abnormalities are observed, reduce the dosage or discontinue administration.

<Reference Information> Company report
Shigeo Hirai, et al.: Psychiatry and Clinical Neuroscience 1995;37(7):737-742 (in Japanese)

3 <Psychotropics> Chlorpromazine Hydrochloride/Promethazine Hydrochloride/Phenobarbital

[Brand Name] Vegetamin Tablets-A, Vegetamin Tablets-B (Shionogi & Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Aplastic anaemia, haemolytic anaemia, platelets decreased, and agranulocytosis:** Aplastic anaemia, haemolytic anaemia, platelets decreased, and agranulocytosis may occur. Patients should be carefully monitored, and if abnormalities are observed, reduce the dosage or discontinue administration.

<Reference Information> Company report
Shigeo Hirai, et al.: Psychiatry and Clinical Neuroscience 1995;37(7):737-742 (in Japanese)

4 <Psychotropics> Levomepromazine Hydrochloride, Levomepromazine Maleate

[Brand Name] Hirnamin Injection (Shionogi & Co., Ltd.) Levotomin Intramuscular Injection 25 mg (Mitsubishi Pharma Corporation)
Hirnamin Powder 50%, Hirnamin Fine Granules 10%, Hirnamin Tablets (5 mg), (25 mg), and (50 mg) (Shionogi & Co., Ltd.), Levotomin Powder 10% and 50%, Levotomin Granules 10%, Levotomin Tablets 5 mg, 25 mg, and 50 mg (Mitsubishi Pharma Corporation) and others

[Adverse Reactions (clinically significant adverse reactions)] **Aplastic anaemia and agranulocytosis:** Aplastic anaemia and agranulocytosis may occur. Patients should be carefully monitored, and if abnormalities are observed, reduce the dosage or discontinue administration.

<Reference Information> Company report
Shigeo Hirai, et al.: Psychiatry and Clinical Neuroscience 1995;37(7):737-742 (in Japanese)

5 <Diuretics> Spironolactone

[Brand Name] Aldactone-A Fine Granules, Aldactone-A Tablets, Aldactone-A Tablets 50 mg (Pfizer Japan Inc.), and others

[Contraindications] Patients with Addison's diseases

[Important Precautions] Since electrolyte abnormality such as hyperkalaemia may occur in chronic administration, periodic testing should be conducted. Extra caution should be exercised for elderly and patients with decreased renal function or using concomitant medications that may induce hypokalaemia.
Dizziness etc. due to hypotensive action may occur. Patients should be cautioned against operating machines with hazardous activities such as working at heights and driving a car.

<Reference Information> Company report

6 <Protein and amino acid preparations> Aminoleban EN

[Brand Name] Aminoleban EN (Otsuka Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hypoglycaemia**: Hypoglycaemia (cold sweat, feels poorly, tremor, palpitations, etc) may occur. If these symptoms occur, appropriate measures should be taken.

<Reference Information> Company report

7 <Blood and body fluid agents-Miscellaneous>
Sarpogrelate Hydrochloride

[Brand Name] Anplag Fine Granules 10%, Anplag Tablets 50 mg and 100 mg (Mitsubishi Pharma Corporation)

[Adverse Reactions (clinically significant adverse reactions)] **Agranulocytosis**: The patient should be carefully observed, since agranulocytosis may occur. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

8 <Antidotes>
Levofolinate Calcium

[Brand Name] Isovorin Injection 25 mg (Wyeth K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Hyperammonaemia:** Hyperammonaemia accompanying consciousness disturbed may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.
Acute pancreatitis: Acute pancreatitis may occur. Patients should be carefully monitored. If abdominal pain and serum amylase increased etc. are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

9 <Antimetabolites>
Tegafur/Gimeracil/Oteracil Potassium

[Brand Name] TS-1 Capsule 20 and 25 (Taiho Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Acute pancreatitis:** Acute pancreatitis may occur. Patients should be carefully monitored. If abdominal pain and serum amylase increased etc. are observed, administration should be discontinued and appropriate measures should be taken.
Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feelings of weakness, CK (CPK) increased and myoglobin blood increased and urine myoglobin increased may occur. Discontinue administration and take appropriate measures in such cases. Caution should be exercised for the onset of acute renal failure resulting from rhabdomyolysis.

<Reference Information> Company report

10 <Acting mainly on gram-positive bacteria, gram-negative bacteria, rickettsia and chlamydia>
Minocycline Hydrochloride (oral dosage form, injectable dosage form)

[Brand Name] Minomycin Granules, Minomycin Capsules 50 mg and 100 mg, Minomycin Tablets 50 mg and 100 mg, Minomycin Intravenous (for Drip Use) (Wyeth K.K.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Enterocolitis haemorrhagic and pseudomembranous colitis:** Serious enterocolitis such as enterocolitis haemorrhagic and pseudomembranous colitis etc. may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued immediately and appropriate measures should be taken.

<Reference Information> Company report

11 <Synthetic antibacterials> Linezolid

[Brand Name] Zyvox Tablets 600 mg, Zyvox Injection 600 mg (Pfizer Japan Inc.)

[Important Precautions] Optic nerve disorder may occur and it may progress to vision loss when this drug is administered over a period of 28 days. Patients should be carefully monitored. If subjective symptoms such as visual acuity reduced, defective colour vision, vision blurred, and visual field defect are observed, patients should be instructed to contact a physician immediately. If these symptoms occur, appropriate measures such as discontinuation of administration should be taken.

[Adverse Reactions (clinically significant adverse reactions)] **Shock and anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. If abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

<Reference Information> Company report

12 <Chemotherapeutics-Miscellaneous> Terbinafine Hydrochloride (oral dosage form)

[Brand Name] Lamisil Tablets 125 mg (Novartis Pharma K.K.)

[Important Precautions] Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored during administration of this drug.

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), and acute generalised exanthematous pustulosis:** Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

13 Over the counter drugs Famotidine-containing Product

[Brand Name] Gaster 10, Gaster Powder (Zepharma Inc.)

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or your pharmacist for consultation.

If the following symptoms are observed after taking this drug

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.

Rhabdomyolysis: Pain and stiffness of muscle in the extremities or body may occur. Colour of urine may become reddish brown.

<Reference Information> Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of December 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Bosentan Hydrate / Tracleer Tablets 62.5 mg	Actelion Pharmaceuticals Japan Ltd.	June 10, 2005
Tamibarotene / Amnolake Tablets 2 mg	Toko Pharmaceutical Industrial Co., Ltd.	June 13, 2005
Tocilizumab (Genetical recombination) / Actemra for Intravenous Infusion 200	Chugai Pharmaceutical Co., Ltd.	June 13, 2005
Adenosine / Adenoscan Injection 60 mg	Daiichi Suntory Pharma Co., Ltd.	June 21, 2005
Voriconazole / Vfend Tablets 50 mg and 200 mg, Vfend 200 mg for Intravenous Use	Pfizer Japan Inc.	June 27, 2005
Luliconazole / Lulicon Cream 1%, Lulicon Solution 1%	Pola Chemical Industries, Inc.	July 20, 2005
Fludeoxyglucose / FDGscan Injectable	Nihon Medi-Physics Co., Ltd.	August 1, 2005
Fludeoxyglucose / FDGscan-MP Injectable	The Medical and Pharmacological Research Center Foundation	August 1, 2005
Monteplase (Genetical recombination) / Cleactor Injection 400000, 800000, and 1600000[*1]	Eisai Co., Ltd.	August 5 2005
Follitropin Beta (Genetical recombination) / Follistim Inj. 75 and 150	Nippon Organon K.K.	August 11, 2005
Doripenem Hydrate / Finibax 0.25 g IV Solution	Shionogi & Co., Ltd.	September 16, 2005
Dehydrated Ethanol / Anhydrous Ethanol Injection “Fuso”	Fuso Pharmaceutical Industries, Ltd.	September 16, 2005
Dehydrated Ethanol / Dehydrated Ethanol Inj. “Merck”	Merck Pharma Ltd.	September 20, 2005
Pilocarpine Hydrochloride / Salagen Tab. 5 mg	Kissei Pharmaceutical Co., Ltd.	September 22, 2005
Gemtuzumab Ozogamicin (Genetical recombination) / Mylotarg Injection 5 mg	Wyeth K.K.	September 22, 2005
Alteplase (Genetical recombination) / Activacin for Injection 6000000, 12000000, and 24000000[*2]	Kyowa Hakko Kogyo Co., Ltd.	October 11, 2005
Alteplase (Genetical recombination) / Grtpa Inj. 6000000, 12000000, and 24000000[*2]	Mitsubishi Pharma Corporation	October 11, 2005

Candesartan Cilexetil Blopress Tablets 2, 4, and 8[*3]	Takeda Pharmaceutical Company Limited	October 11, 2005

Note) Subject to additional indications etc.

*1: An additional indication for "lysis of pulmonary thrombosis of acute pulmonary embolism accompanied with unstable homodynamic"

*2: An additional indication for "the improvement of dysfunction in the acute stage of ischemic cerebrovascular disease (within 3 hours of onset)"

*3: An additional indication for "the treatment of patients in the condition of chromic cardiac failure (mild to moderate) for which administration of angiotensin converting enzyme (ACE) inhibitors is not appropriate"