Pharmaceuticals and Medical Devices Safety Information

No. 207 November 2004

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

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 after the issue before previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 205), together with reference materials.

1 Paclitaxel

Brand Name (name of company)	Taxol Injection (Bristol Pharmaceuticals Y.K.)
Therapeutic Category	Antineoplastic plant extract preparations
Indications	Ovarian cancer, non-small cell lung cancer, breast cancer, gastric cancer

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

[Important Precautions]

As this drug contains dehydrated ethanol, the interaction between alcohol and diphenhydramine hydrochloride tablets administered as premedication may intensify the effect of central nervous system depression. Patients should be monitored for their course after administration. If the effects of alcohol etc. are suspected, patients should be advised to refrain from potentially hazardous activities including driving while taking this drug.

[Adverse Reactions (clinically significant adverse reactions)]

Myocardial infarction, cardiac failure congestive, cardiac conduction disorders, pulmonary embolism, thrombophlebitis, cerebral apoplexy, pulmonary oedema: Myocardial infarction, cardiac failure congestive, cardiac conduction disorders, pulmonary embolism, thrombophlebitis, cerebral apoplexy, and pulmonary oedema may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued.

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

Serious enterocolitis: Colitis haemorrhagic, pseudomembranous colitis, and colitis ischaemic etc. may occur. Patients should be carefully monitored. If severe abdominal pain and diarrhoea etc. are observed, administration should be discontinued and appropriate measures should be taken.

Intestinal obstruction, paralysis intestinal: Intestinal obstruction and paralysis intestinal (anorexia, nausea and vomiting, significant constipation, abdominal pain, abdominal distension or abdominal flaccidity, and stagnation of intestinal contents, etc.) resulting in ileus paralytic may occur. If intestinal obstruction or paralysis intestinal are observed, administration should be discontinued and appropriate measures, such as intestinal decompression etc. should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 50s	Ovarian cancer (hypertension, diabetes mellitus, hypothyroidism)	232 mg 1 day	**Gastrointestinal necrosis** 138 days before administration: The patient received cytoreductive surgery at another hospital. 111 days before administration: First course of chemotherapy (240 mg of this drug + 910 mg of carboplatin) was conducted. 90 days before administration: Second course of chemotherapy (240 mg of this drug + 900 mg of carboplatin) was conducted. 73 days before administration: Platelet count decreased to $2 \times 10^4/mm^3$. 62 days before administration: Third course of chemotherapy (240 mg of this drug + 900 mg of carboplatin) was conducted. Major adverse reactions: numbness, myalgia, white blood cell decreased ($1400/mm^3$ 18 days after administration) 28 days before administration: Implemented interval cytoreductive surgery was performed. Postoperative course was good. Definite diagnosis: There was no residual tumor and lymph node metastases; advanced stage Ic (b) On day 1 of administration: Fourth course of chemotherapy (232 mg of this drug + 600 mg of carboplatin) was conducted. 5 days after administration: Bowel movements were insufficient after administration and did not respond to laxatives or enema. Lower abdominal pain manifested at around midday which gradually intensified, although no abdominal abnormalities were found. 6 days after administration: The patient vomited 2 times during the night. Pain was mitigated with pentazocine. Although X-ray showed gas build-up in the transverse colon, niveau was not confirmed. CT scan confirmed similar findings. However, the abdominal pain 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 (to 50-80/32-45 mmHg), DOA administration was commenced. Blood samples were taken as follows: at noon, white blood cell count was $4500/mm^3$, platelet count was $14 \times 10^4/mm^3$; at night, white blood cell count was $2300/mm^3$, platelet count was $5.6 \times 10^4/mm^3$; 1 hour later, white blood cell count was $1100/mm^3$ and progression of DIC was surmised. Another 1 hour later, emergency surgery was conducted (subtotal colectomy, colostomy, adhesiolysis: amount of haemorrhage 5480 mL).	Company report

				7 days after administration: Immediate postoperative white blood cell count and platelet count were 300/mm^3 and 0.3×10^4/mm^3, respectively. Although blood transfusion was continued, the bloody drainage continued. 8 days after administration: The patient unable to break away from DIC and bleeding tendency continued (white blood cell count was 500/mm^3 and platelet count was 0.1×10^4/mm^3). Pleural effusion was accumulated. 9 days after administration: Atrial fibrillation occurred. Although defibrillation was conducted, the patient went into cardiac arrest. Pulse recovered through resuscitation. As there was increase in pleural effusion, bilateral thoracic drainage was conducted and effusion pleural bloody was suctioned. Elevation in hepatic enzymes surmised to be caused by congestive liver disorder. 10 days after administration: Systemic petechiae and oedema developed. There was insufficient urinary retention and acidosis progressed. 11 days after administration: The patient died (direct cause of death was multi-organ failure from DIC due to intestinal necrosis).	
	Concomitant medications: carboplatin, omeprazole, mosapride citrate, sucralfate, thiamazole, amlodipine besilate, voglibose, mecobalamin, magnesium oxide, etizolam				

Clinical Laboratory Values

	Before admin.	5 days after admin.	6 days after admin.		7 days after admin.	8 days after admin.	9 days after admin.
RBC ($\times10^4$/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	300	500	300
Neutrophils (%)	85.8	74.7			38.0	20.0	21.0
PLT ($\times10^4$/mm^3)	32.2	22.6	14.0	5.6	0.3	0.1	0.5
Pt (seconds)	--	--	--	--	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
Pt: Prothrombin time
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	
2	Female 30s	Recurrent ovarian cancer (none)	180 mg 1 day	**Intestinal obstruction** 53 days before administration: Surgery was conducted (simple total hysterectomy, adnexectomy, intrapelvic lymph nodes dissection). 48 days before administration: Mild intestinal obstruction developed after surgery and improved 2 days later. (fasting only) On day 1 of administration: Second course of chemotherapy (180 mg of this drug, 450 mg of carboplatin) was performed. 3 days after administration: Recurrence of symptoms of intestinal obstruction (mild). The symptoms did not improve through conservative treatment. 11 days after administration: White blood cell decreased developed. It was recovered without symptoms through lenograstim administration (SC 100 μg for 3 days). 15 days after administration: White blood cell decreased. 17 days after administration: The patient was hospitalized. The symptoms worsened. 22 days after administration: Strangulation ileus (surgery) was performed (concurrent excision of small intestine and large intestine could not be performed). 50 days after administration: The patient was discharged from the hospital. She is currently receiving out-patient treatment. Strangulation of ileus is currently resolved.	Company report
	Concomitant medications: carboplatin, dexamethasone sodium phosphate, ranitidine hydrochloride, tropisetron hydrochloride, diphenhydramine hydrochloride				

Clinical Laboratory Values

	4 days before admin.	7 days after admin.	11 days after admin.	13 days after admin.	15 days after admin.	17 days after admin.
RBC ($\times 10^4/mm^3$)	387	387	340	365	358	371
Haemoglobin (g/dL)	11.9	11.7	10.3	11.4	11.3	11.4
WBC ($/mm^3$)	3600	2200	1100	1700	6700	4900
PLT ($\times 10^4/mm^3$)	17.0	18.0	17.9	17.4	17.1	14.6
AST (GOT) (IU/L)	29	39	--	--	49	56
ALT (GPT) (IU/L)	40	70	--	--	56	84
Al-P (IU/L)	158	147	--	--	178	192
LDH (IU/L)	471	469	--	--	575	613
γ-GPT (IU/L)	137	130	--	--	110	127
Total bilirubin (mg/dL)	0.7	1.0	--	--	--	0.3
Serum Na (mEq/L)	144	141	--	--	145	145
Serum K (mEq/L)	4.1	4.2			3.9	3.6
Serum Cl (mEq/L)	106	105	--	--	107	105
BUN (mg/dL)	13	12	--	--	8	10
Serum creatinine (mg/dL)	0.63	0.62	--	--	0.69	0.57
CRP (mg/dL)	--	0.16	--	--	--	0.16

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 60s	Non-small cell lung cancer (hyperlipidaemia, constipation)	326 mg 1 day	**Ileus paralytic** On day 1 of administration: Chemotherapy (326 mg of this drug, 594 mg of carboplatin) was started. 5 days after administration: There were no symptoms of particular note until the morning. Vomiting manifested from the evening. 60 mg of domperidone suppository was administered. Ileus paralytic and acute renal failure developed. 6 days after administration: Urinary retention started before dawn although there was desire for urination since nighttime. Several times of vomiting and abdominal pain developed. On the other hand, bowel movements and expulsion of gas was no longer confirmed. Upon palpation of the abdominal region by her physician, there was significant tenderness and as abdominal noises were not heard, ileus paralytic was suspected. Systolic blood pressure: shifting between 70-100 mmHg; blood test: severe dehydration; blood gas: metabolic acidosis; chest X-ray: no change was confirmed; abdominal X-ray: toxic megacolon was suspected. Although urethral catheter was inserted, there was no urination. It was surmised that fluid accumulation in the paralyzed intestinal tract resulted in intravascular volume depletion. Physiological saline and 5% glucose solution were administered to compensate for the dehydration. Intravenous drip of sodium bicarbonate was tried to correct metabolic acidosis. However, there was no urination and intravenous administration of furosemide was implemented. Administration of dopamine hydrochloride was started at 3 μg for the purpose of the improvement of renal blood flow. As for the treatment of the ileus paralytic, a digestive organ specialist attempted to reduce the pressure by inserting an ileus tube under fluoroscopic guidance. Although fluid replacement was continued through the central venous catheter, urination was not achieved. From around the night, abdominal pain significantly worsened. Blood pressure 100/60 mmHg was confirmed. Although intramuscular injection of 7.5 mg of pentazocine was conducted, abdominal pain intensified. Depressed level of consciousness, decreased breath sounds, and symptoms of shock were confirmed.	Company report

				Intratracheal intubation, initiation of artificial respiration, administration of etilefrine hydrochloride, increase in dosage of dopamine hydrochloride, and concurrent administration of dobutamine hydrochloride were conducted in cooperation with the physician on duty. Heart rate decreased was confirmed, and intravenous injection of epinephrine was conducted. Afterwards, decreased heart rate followed by intravenous injection of epinephrine was repeated. As it was judged that effective cardiac output was not being derived, cardiac massage was conducted concurrently. But the response gradually decreased. 7 days after administration: Death was confirmed by absence of spontaneous respiratory and cardiac functions and loss of pupillary reflex. (cause of death: acute renal failure, autopsy: not performed)	
	Concomitant medications: carboplatin, loxoprofen sodium, spironolactone, furosemide, ranitidine hydrochloride, rebamipide, sennoside, ramosetron hydrochloride, dexamethasone sodium phosphate, diphenhydramine hydrochloride				

Clinical Laboratory Values

		15 days before admin.	1 day before admin.	4 days after admin.	6 days after admin.
RBC ($\times 10^4$/mm^3)		390	407	382	478
Haemoglobin (g/dL)		11.6	12.0	11.4	14.4
Haematocrit (%)		34.6	36.6	34.4	43.0
WBC (/mm^3)		9110	9150	8090	9400
Differential white blood cell count	Eosinophils (%)	7.1	9.0	0.5	1.3
	Neutrophils (%)	60.9	57.0	73.1	83.0
	Basophils (%)	1.2	1.1	0.5	1.0
	Lymphocytes (%)	22.5	24.5	22.0	13.1
	Monocytes (%)	6.8	7.0	3.2	1.3
PLT ($\times 10^4$/mm^3)		43.1	42.6	40.5	41.5
MCV (FL)		88.8	89.8	90.1	90.0
MCH (pg)		29.6	29.5	29.8	30.2
MCHC (g/dL)		33.4	32.9	33.0	33.6
Luc (%)		1.5	1.3	0.8	0.3
AST (GOT) (IU/L)		16	15	18	54
ALT (GPT) (IU/L)		11	10	12	42
Al-P (IU/L)		247	261	--	--
LDH (IU/L)		175	184	--	294
Total bilirubin (mg/dL)		0.3	0.3	0.5	1.0
Serum Na (mEq/L)		141	139	136	133
Serum K (mEq/L)		4.2	4.4	4.9	5.3
Serum Ca (mg/L)		10.7	10.9	--	11.5
Serum creatinine (mg/dL)		0.8	1.0	0.9	1.3
Total protein (g/dL)			9.1		9.2
Albumin (g/dL)		3.6	3.8	--	4.0
Glucose (mg/dL)		90	--	--	189
A/G 0.71		0.71	--	--	0.76
UA (mg/dL)		8.6	--	--	--
CRP (mg/dL)		5.4	5.9	2.8	4.3

RBC: Red Blood Cell	AST: Asparate Aminotransferase
WBC: White Blood Cell	ALT: Alanine Aminotransferase
PLT: Platelet	Al-P: Alkaline Phosphatase
MCV: Mean Corpuscular Volume	LDH: Lactate Dehydrogenase
MCH: Mean Corpuscular Haemoglobin	A/G: Albumin/Globulin Ratio
MCHC: Mean Corpuscular Hemoglobin Concentration	UA: Uric Acid
Luc: Large Unstained Cells	CRP: C-Reactive Protein

2 Sodium Rabeprazole

Brand Name (name of company)	Pariet Tablets 10 mg and 20 mg (Eisai Co., Ltd.)
Therapeutic Category	Peptic ulcer agents
Indications	Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis and Zollinger-Ellison syndrome

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

[Adverse Reactions (clinically significant adverse reactions)]

Pancytopenia, agranulocytosis, thrombocytopenia and hemolytic anemia: Pancytopenia, agranulocytosis, thrombocytopenia and hemolytic anemia may occur. Patients should be carefully monitored, and if such abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Fulminant hepatitis, hepatic function disorders and jaundice: Fulminant hepatitis, hepatic function disorders and jaundice may occur. Patients should be carefully monitored, and if such abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Toxic epidermal necrolysis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme: Dermatopathies such as toxic epidermal necrolysis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme may occur. Patients should be carefully monitored, and if such abnormalities are observed, treatment should be discontinued and appropriate measures should be taken.

Interstitial pneumonia: Interstitial pneumonia may occur Caution should be exercised with respect to renal function tests (BUN, creatinine, etc.). If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 70s	Gastrointestinal ulcer haemorrhage (hepatitis C, angina pectoris)	20mg 5 days	**Haemolytic anaemia** 6 days before administration: As there was stool tarry and a small amount of haematemesis, the patient was examined by a nearby physician. As significant anaemia was confirmed with a haemoglobin level of 6.7 g/dL in a blood sample, she was transported to this hospital by ambulance and hospitalized. Emergency endoscopy confirmed gastric ulcer extending from the upper body of the stomach to the posterior wall of middle body of the stomach. Although blood clots were observed in the stomach, as there was no active haemorrhage, treatment was not implemented. 6 units of concentrated human red blood cells were transfused. 3 days before administration: When gastroendoscopy of the upper tract was conducted for the purpose of re-inspection, as spurting haemorrhage from the ulcerous area was confirmed, local injection of hypertonic sodium epinephrine solution and clipping were conducted to stop the haemorrhage. 2 days before administration: Gastroendoscopy was re-conducted and it was confirmed that the haemorrhage had stopped. At this point, there was no haemorrhage and haemoglobin level was 10.0 g/dL. On day 1 of administration: Together with starting a liquid diet, oral administration of this drug was started. On day 5 of administration (day of discontinuation): The patient suddenly had brown urine. Administration of this drug was discontinued. Gastric ulcer improved to H_1 stage, thereafter course was good. 1 day after discontinuation: Based on the increases in red blood cell count 287 × 10^4/mm^3, haemoglobin 8.7 g/dL, LDH 2988IU/L (only LDH I and LDH II increased: LDH I type 34%, LDH II type 36%), total bilirubin 1.8 mg/dL, direct bilirubin 0.4 mg/dL, the patient was diagnosed with haemolytic caused by this drug. Administration of ranitidine hydrochloride at 150 mg was started. 2 days after discontinuation: Red blood cell count 261 × 10^4/mm^3, haemoglobin 7.9 g/dL, LDH 2471 IU/L (LDH I type 33%, LDH II type 37%), reticulocytes 39.1‰, haptoglobin 10 mg/dL or less. Coombs test: direct (−), indirect (4+). 3 days after discontinuation: Red blood cell count 240 × 10^4/mm^3, haemoglobin 7.1 g/dL, LDH 1746 IU/L, and total bilirubin 0.4 mg/dL. 14 days after discontinuation: Although X-ray barium enema was conducted, there were no abnormal findings. Red blood cell count 426 × 10^4/mm^3, haemoglobin 13.0 g/dL, LDH 687 IU/L, total bilirubin 0.6 mg/dL.	Company report

				16 days after discontinuation: Haemolytic anemia was recovered and the patient was discharged from the hospital. 29 days after discontinuation: Red blood cell count 402 × 10^4/mm^3, haemoglobin 12.2 g/dL, LDH 460 IU/L, and reticulocytes 9.7%$_0$. After discontinuation of this drug, brown urine disappeared and anaemia did not progress. Thereafter, oral administration was replaced by 150 mg of ranitidine hydrochloride and condition was monitored. There was no brown urine or progression of anaemia.	
	Concomitant medications: teprenone, amlodipine besilate, isosorbide mononitrate, sulpiride, triazolam				

Clinical Laboratory Values

	6 days before admin.	3 days before admin.	On day 4 of admin.	1 day after discontinuation	3 days after discontinuation	6 days after discontinuation	14 days after discontinuation	29 days after discontinuation
WBC (/mm^3)	12000	5300	7400	5500	5400	3800	5700	6400
RBC (×10^4/mm^3)	222	331	321	287	240	390	426	402
Haemoglobin (g/dL)	6.7	9.8	9.6	8.7	7.1	11.6	13.0	12.2
Haematocrit (%)	19.6	29.7	29.3	25.8	21.9	35.4	39.4	36.5
MCV (FL)	--	89.7	91.3	89.9	91.3	90.8	92.5	--
PLT (×10^4/mm^3)	18.6	23.0	26.8	13.5	13.0	19.2	24.8	20.6
AST (GOT) (IU/L)	20	24	27	53	27	22	25	--
ALT (GPT) (IU/L)	16	21	21	18	20	22	31	--
Al-P (IU/L)	165	173	238	193	188	202	257	--
LDH (IU/L)	343	399	930	2988	1746	1167	687	460
γ-GPT (IU/L)	18	23	24	19	20	22	25	--
Total bilirubin (mg/dL)	0.3	0.5	1.3	1.8	0.4	0.6	0.6	--
CRP (mg/dL)	3.4	0.8	0.7	9.0	3.1	1.8	0.4	

WBC: White Blood Cell
RBC: Red Blood Cell
MCV: Mean Corpuscular Volume
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 70s	Upper abdominal pain (diabetes mellitus, hyperlipidaemia)	Unknown 5 days	**Hepatitis fulminant** Approx. 2 weeks before administration: The patient started feeling ill from around this time. He had previously been going to a nearby physician for treatment of diabetes mellitus and hyperlipidaemia. 2 days before administration: The patient received health checkup. AST (GOT) and ALT (GPT) were both 13 IU/L. On day 1 of administration: H_2 blocker which was prescribed until this time was replaced by this drug. On day 5 of administration (day of discontinuation): The patient was examined at this hospital. He complained of breathing difficulty and anuria. AST (GOT) 8253 IU/L, ALT (GPT) 4395 IU/L, total bilirubin 3.58 mg/dL, LDH 7425 IU/L, ammonia 197 μg/dL, white blood cell count 20800/mm^3. The patient had tendency toward somnolence, conjunctiva bulbi colouring yellow, and mild jaundice. CT and echogram did not confirm hepatic atrophy. Virus tests were both negative for HCV and HBs antigens. 1 day after discontinuation: There were findings of hepatic encephalopathy. Coma scale shifted from level I to II in the afternoon to level III at night. Prothrombin time was 16%. AST (GOT) and ALT (GPT) levels decreased from the previous day to 5376 IU/L and 4008 IU/L, respectively. 2 days after discontinuation: The patient died of cardiac tamponade. Autopsy results: there were findings of congestion of the liver and the possibility of cardiac failure congestive as the cause of death cannot be denied.	Company report
	Concomitant medications: glimepiride, hyperlipidaemia agent				

Clinical Laboratory Values

	On day 5 of admin. (day of discontinuation)	1 day after discontinuation
Pt (seconds)	--	32.1
Pt (%)	--	16
PT-INR	--	4.59
APTT (seconds)		40.6
AST (GOT) (IU/L)	8253	5376
ALT (GPT) (IU/L)	4395	4008
Al-P (IU/L)	274	298
LDH (IU/L)	7425	4379
γ-GPT (IU/L)	166	160
LAP (U/L)	114	105
Total bilirubin (mg/dL)	3.58	3.78
Total protein (g/dL)	7.4	6.9
Albumin (g/dL)	4.1	3.8

CPK (IU/L)	830	1115
CK-MB (IU/L)	25	--
BUN (mg/dL)	66.7	88.3
Serum creatinine (mg/dL)	1.6	2.5
Urate (mg/dL)	17.0	15.6
Na (mEq/L)	130	129
K (mEq/L)	5.5	5.7
Cl (mEq/L)	93	90

Pt: Prothrombin Time
PT-INR: Prothrombin Time-International Normalized Ratio
APTT: Activated Partial Thromboplastin Time
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
LAP: Leucine Aminopeptidase
CPK: Creatine Kinase
CK-MB: Creatine Kinase MB Isoenzyme
BUN: Blood Urea Nitrogen
Na: Sodium
K: Potassium
Cl: Chloride

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 50s	Gastrointestinal ulcer haemorrhage (chronic renal failure, diabetes mellitus, atrioventricular block second degree)	10 mg 7 days	**Hepatitis fulminant** 1 day before administration: The patient was hospitalized for haematocrit value decreased, and diagnosed with A_2 stage gastric ulcer based on gastroendoscopy. Blood transfusion was given, treatment with sodium alginate and thrombin was started. On day 5 of administration: 6 units of concentrated human red blood cells were transfused and although anaemia was showing tendency toward improvement, hepatic function disorder was started to develop. AST (GOT) 62 IU/L, ALT (GPT) 52 IU/L. Treatment with a glycyrrhizin preparation was started. On day 7 of administration (day of discontinuation): Significant hepatic function disorder developed. AST (GOT) 1253 IU/L, ALT (GPT) 655 IU/L, LDH 3954 IU/L, total bilirubin 1.66 mg/dL. Treatment with this drug was discontinued. 2 days after discontinuation: Hepatic function aggravated. Concomitant medications other than sodium alginate were discontinued. Hypocoagulability and platelet count decreased were confirmed and the hepatitis fulminant developed. Plasma exchange was conducted. 3 days after discontinuation: Transfusion of 10 units of platelets (similarly 5 and 7-11 days after discontinuation) and plasma exchange (similarly 5, 7, and 9 days after discontinuation) were conducted. 43 days after discontinuation: Hepatic function gradually recovered and the patient was discharged from the hospital.	Company report
	Concomitant medications: verapamil hydrochloride, sodium alginate, thrombin, digoxin, precipitated calcium carbonate, amezinium metilsulfate, calcitriol, niceritrol, aprindine hydrochloride				

Clinical Laboratory Values

	1 day before admin.	On day 5 of admin.	On day 7 of admin. (day of discontinuation)	2 days after discontinuation	3 days after discontinuation	7 days after discontinuation	35 days after discontinuation
Pt (%)	--	--	--	34	--	50	67
Hepaplastin test (%)	--	--	--	28	--	41	59
AST (GOT) (IU/L)	10	62	1253	2708	1051	313	14
ALT (GPT) (IU/L)	12	52	655	1809	804	264	8
Al-P (IU/L)	256	253	--	293	203	227	319
LDH (IU/L)	345	630	3954	4448	1276	673	382
γ-GPT (IU/L)	--	--	--	129	20	30	--
Total bilirubin (mg/dL)	0.23	0.56	1.66	3.46	2.52	2.17	0.92
Direct bilirubin (mg/dL)	0.09	--	--	2.16	1.52	1.19	0.61
Total protein (g/dL)	5.3	5.8	5.9	6.2	5.1	5.8	6.6
HBs antigen	(–)	--	--	(–)	--	--	--
HBs antibody (PHA method)	--	--	--	(–)	--	--	--
HBc antibody (EIA method)	--	--	--	9	--	--	--
IgM-HBc	--	--	--	0.1	--	--	--
HCV antibody (3rd)	(–)	--	--	--	--	--	--
HCV-RNA	--	--	--	(–)	--	--	--
DNA polymerase	--	--	--	3	--	--	--
CMV CF	--	--	--	--	16	--	--
CMV IgG					78.3 (+)		
CMV IgM	--	--	--	--	0.22 (–)	--	--
EBV VCA IgG	--	--	--	--	160	--	--
EBV VCA IgM	--	--	--	--	less than 10	--	--
EBV VCA IgA					10		
EBV EA-DR IgG	--	--	--	--	less than 10	--	--
EBV EA-DR IgA	--	--	--	--	less than 10	--	--
EBV EBNA	--	--	--	--	10	--	--

Pt (%): Prothrombin Activity (%)
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
HBs: Hepatitis Virus Bs
HBc: Hepatitis Virus Bc
IgM-HBc: IgM Hepatitis Virus Bc Antibody
HCV: Hepatitis C Virus
DNA: Deoxyribonucleic Acid
CMV CF: Cytomegalovirus Complement Fixation
CMV IgG: Cytomegalovirus Immunoglobulin G
CMV IgM: Cytomegalovirus Immunoglobulin M
EBV VCA IgG: Epstein-Barr Virus, Viral Capsid Antigen Antibody Immunoglobulin G
EBV VCA IgM: Epstein-Barr Virus, Viral Capsid Antigen Antibody Immunoglobulin M
EBV VCA IgA: Epstein-Barr Virus, Viral Capsid Antigen Antibody Immunoglobulin A
EBV EA-DR IgG: Epstein-Barr virus, Early Antigen-Diffuse and Restricted Antibody Immunoglobulin G
EBV EA-DR IgA: Epstein-Barr virus, Early Antigen-Diffuse and Restricted Antibody Immunoglobulin A
EBV EBNA: Epstein-Barr Virus, Nuclear Antigen Antibody

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 70s	Gastric ulcer (anxiety neurosis, common cold, sick sinus syndrome)	20 mg 22 days ↓ (no treatment for 20 days) ↓ 20 mg 6 days	**Erythema multiforme** On day 1 of administration: Treatment with this drug was started to treat recurrent gastric ulcer. On day 12 of administration: Erythema multiforme manifested on lower legs. According to the patient, as erythema multiforme tends to appear after treatment wiht 1 mg paramethasone acetate, treatment with this drug was discontinued from the evening of the same day and replaced by 15 mg prednisolone. On day 17 of administration: Rash appeared on the upper legs as well. On day 22 of administration (day of discontinuation): Rash on arms and legs further aggravated. Some formed blister. Treatment with this drug, levodopa, diclofenac sodium, verapamil hydrochloride, and ticlopidine hydrochloride were discontinued. 2 days after discontinuation: The symptoms ceased to progress and subsided. 21 days after discontinuation (on day 1 of readministration): As gastroendoscopy confirmed recurrence of gastric ulcer, treatmenm with this drug was recommenced. On day 6 of readministration (day of discontinuation): The aforementioned rash reappeared on lower legs. Treatmenm with this drug was discontinued. 6 days after discontinuation: Rash disappeared.	Company report
	Concomitant medications: verapamil hydrochloride, amitriptyline hydrochloride, ticlopidine hydrochloride, diclofenac sodium, vinpocetine, paramethasone acetate, vitamin B complex, mequitazine, levodopa				

2

Revision of PRECAUTIONS

(No. 160)

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 issue before previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 205) (excluding those presented in "1. Important Safety Information" of this Bulletin.), together with reference materials.

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1 **<Antipyretics and analgesics, anti-inflammatory agents>**

Flurbiprofen (oral dosage form)

[Brand Name]	Froben, Froben Gr. (Kaken Pharmaceutical Co., Ltd.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Asthmatic attack:** Asthmatic attack may be induced. If initial symptoms such as wheezing or feeling of dyspnoea etc. are observed, administration should be discontinued.
<Reference Information>	Company report

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2 **<Antipyretics and analgesics, anti-inflammatory agents>**

Flurbiprofen Axetil

[Brand Name]	Ropion Injection (Kaken Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Asthmatic attack:** Asthmatic attack may be induced. If initial symptoms such as wheezing or feeling of dyspnoea etc. are observed, administration should be discontinued.
<Reference Information>	Company report

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3 **<Antiparkinsonian agents>**

Pergolide Mesilate

[Brand Name]	Permax Tablets 50 μg and 250 μg (Eli Lilly Japan K.K.)
[Careful Administration]	Patients with Raynaud disease

[Important Precautions]	"Caution should be exercised when administering, as drug may cause fibrosis (lung, retroperitoneal, etc.)." was omitted. Since it has been reported that cardiac valvulopathy and fibrosis occurring during the administration of ergot preparations including this drug in many cases compared to non-ergot preparations, this drug should be administrated by balancing risks and benefits for each patient. Before starting administration of this drug, it is desirable to check for the presence/absence of potential cardiac valvulopathy through physical examinations such as auscultation and through echocardiography etc. Cardiac valvulopathy and fibrosis may occur. Patients should be carefully monitored (physical examination, X-ray, echocardiography, and CT scan, etc.) during the administration of this drug as appropriate.
<Reference Information>	Company report

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4 **<Hyperlipidaemia agents>**

Bezafibrate

[Brand Name]	Bezatol SR Tab. 100 mg and 200 mg (Kissei Pharmaceutical Co., Ltd.), and others
[Careful Administration]	Patients receiving sulfonylurea hypoglycaemic agents (glibenclamide, gliclazide, glimepiride etc.), nateglinide, and insulin.
[Adverse Reactions (clinically significant adverse reactions)]	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

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5 **<Urogenital and anal organ agents-Miscellaneous>**

Vardenafil Hydrochloride Hydrate

[Brand Name]	Levitra Tablets 5 mg and 10 mg (Bayer Yakuhin, Ltd.)
[Contraindications]	Patients being administered ritonavir, indinavir, atazanavir, ketoconazole, and itraconazole (drugs which strongly inhibit cytochrome P450 3A4)
[Interactions (contraindications for concomitant use)]	Atazanavir
<Reference Information>	Company report

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6 **<Miscellaneous metabolism agents>**

Pamidronate Disodium

[Brand Name]	Aredia Injection 15 mg and 30 mg (Nihon Ciba-Geigy K.K.)
[Important Precautions]	Patients with a history of thyroid surgery may have hypoparathyroidism that may predispose to hypocalcemia with Aredia. Patients should be carefully monitored for serum calcium levels. Sleepiness, dizziness, and attentiveness decreased, etc. may occur. Patients should be cautioned when performing potentially hazardous tasks, such as operating an automobile or machinery.

[Adverse Reactions (clinically significant adverse reactions)]	Shock, anaphylactoid symptoms (bronchospasm, dyspnoea, wheezing, etc.) Renal failure acute, nephritic syndrome due to focal segmental glomerulosclerosis
<Reference Information>	Company report

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7 **<Antineoplastics-Miscellaneous>**

Gefitinib

[Brand Name]	Iressa Tablets 250 (AstraZeneca K.K.)
[Warning]	**WARNING** While cases of lethal outcome due to acute lung disorders and interstitial pneumonia have been reported regardless of the general condition of patients, incidence and mortality rate tends to increase particularly among patients in poor general condition. Extra caution should be exercised when administering this drug, such as by carefully monitoring the patient's condition.
[Careful Administration]	Patients in poor general condition
<Reference Information>	Company report

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8 **<Acting mainly on gram-positive and gram-negative bacteria>**

Meropenem Trihydrate

[Brand Name]	Meropen for Intravenous Drip Infusion Vial 0.25 g and 0.5 g (Sumitomo Pharmaceuticals Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Pancytopenia, agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia:** Patients should be carefully monitored including periodic hematological tests, and if abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

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9 **<Acting mainly on gram-positive bacteria and mycoplasma>**

Azithromycin Hydrate

[Brand Name]	Zithromac Fine Granules for Pediatric Use, Zithromac Capsules for Pediatric Use 100 mg, Zithromac Tablets 250 mg and 600 mg (Pfizer Japan Inc.)
[Adverse Reactions (clinically significant adverse reactions)	**Acute renal failure:** Acute renal failure may occur. Patients should be carefully monitored. If findings of decreased renal function such as symptoms of oliguria etc. or blood creatinine increased etc. are confirmed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

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10 **< Acting mainly on gram-positive bacteria, Acting mainly on gram-negative bacteria, Acting mainly on gram-positive and gram-negative bacteria, Acting mainly on gram-positive bacteria and mycoplasma, Acting mainly on gram-positive bacteria, gram-negative bacteria, rickettsia and chlamydia, Acting mainly on acid-fast bacteria, Antibiotics-Miscellaneous, Sulfonamides, Synthetic antibacterials>**

Antibiotic Preparations, Sulfonamides, and Synthetic Antibacterials (injection dosage form)

[Important Precautions]	(the entry relating to shock was omitted) Since there is no certain method of predicting the onset of shock or anaphylactoid symptoms caused by this drug, following measures should be taken:

① Sufficiently obtain patient's medical history etc. in advance. In addition, the patient's allergic histories with antibiotics etc. should be confirmed.
② Emergency measures against shock etc. must be prepared prior to administration.
③ Patients should be kept rested throughout administration and carefully monitored. In particular, patients should be carefully monitored immediately after the start of administration.

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11 <Acting mainly on gram-positive and gram-negative bacteria, Sulfonamides>
Antibiotic Preparations and Sulfonamides (suppository dosage form)

[Important Precautions] (the entry relating to shock was omitted)
Since there is no certain method of predicting the onset of shock or anaphylactoid symptoms caused by this drug, sufficiently obtain patient's medical history etc. in advance. In addition, the patient's allergic histories with antibiotics etc. should be confirmed.

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12 <Antivirals>
Atazanavir Sulfate

[Brand Name] Reyataz Capsules 150 mg and 200 mg (Bristol Pharmaceuticals Y.K.)

[Contraindications] Patients receiving the following drugs: rifampicin, irinotecan hydrochloride, midazolam, triazolam, bepridil hydrochloride, ergotamine tartrate, dihydroergotamine mesilate, ergometrine maleate, methylergometrine maleate, cisapride, pimozide, simvastatin, indinavir, proton pump inhibitor, vardenafil hydrochloride hydrate

[Interactions (contraindications for concomitant use)] Vardenafil hydrochloride hydrate

<Reference Information> Company report

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13 <IVD (in vitro diagnostics)>
Blood Glucose Test Kit

[Glucose kits that employ the glucose dehydrogenase method for measurement, with the exception of those that use coenzyme NAD (P)]

[Brand Name] FreeStyle Kissei Sensor, Nipro FreeStyle Sensor (Nipro Corporation), Accu-Chek Compact Drum II, Accu-Chek Active Sticks, Accu-Chek Advantage Test Strips S (Roche Diagnostics K.K.), Glutest Neo Sensor, G Sensor (Matsushita-Kotobuki Electronics Industries, Ltd.), GASTAT-mini Sensor Card for Glucose Measurement (Techno Medica Co., Ltd.), and others

[Warning] The following patients should not be treated with this product, since overestimation of blood glucose levels may occur.
Patients receiving infusions etc. containing maltose
Patients receiving dialysis solution containing icodextrin
Patients undergoing galactose tolerance test
Patients undergoing a xylose absorption test
These items should be written so that they are easy to see relative to other items, such as by using a gothic font etc.

<Reference Information> Company report

14 <Non-main therapeutic purpose agents-Miscellaneous>
Oxygen, Liquid Oxygen

[Brand Name] Oxygen, liquid oxygen, etc.

[Use in Children] There have been epidemiological investigative reports that the incidence of hepatoblastoma will become higher as treatment duration with oxygen is extended in extremely low birth weight infants.

<Reference Information>

Company report
Maruyama, K., et al.: Pediatrics International, 41: 82-89 (1999) (In Japanese)
Maruyama, K., et al.: Pediatrics International, 42: 492-498 (2000)
Takeshi Nagaya, et al.: Journal of Japan Society of Neonatal Medicine, 38(2): 446 (2002) (In Japanese)
Masakazu Miyawaki, et al.: Journal of Japan Society for Premature and Newborn Medicine, 14(2): 201–204 (2002) (In Japanese)