Pharmaceuticals and Medical Devices Safety Information

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is 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).

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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).

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

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Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the "PRECAUTIONS" section of package inserts of drugs that have been revised in accordance with the Notification dated July 6, 2007.

1 Alteplase (Genetical recombination)

Brand Name (name of company)	Activacin for Injection 6000000, 12000000, and 24000000 (Kyowa Hakko Kogyo Co., Ltd.) Grtpa Inj. 6000000, 12000000, and 24000000 (Mitsubishi Pharma Corporation)
Therapeutic Category	Enzyme preparations
Indications	Improvement of dysfunction associated with acute ischemic cerebrovascular disorder (within 3 hours after the onset) Lysis of coronary artery thrombus in acute myocardial infarction (within 6 hours after the onset)

<Reason for revision>

With regard to haemorrhagic adverse reaction of this product, it has been described that "patients treated with this product should be closely monitored for the emergence of haemorrhagic adverse events" in the "WARNING" section of the package insert, and serious haemorrhage such as cerebral haemorrhage (haemorrhage intracranial, etc.), gastrointestinal haemorrhage, pulmonary haemorrhage and retroperitoneal haemorrhage in the Important Precautions and Clinically significant adverse reactions sections as well. In addition, "patients who are haemorrhaging" and "patients who have a high risk of haemorrhage" have been added in the "CONTRAINDICATIONS" section. Recently, MHLW has received reports of cases in which aggravation of thoracic aortic dissection and development of thoracic aortic aneurysm rupture have occurred following use of this product in patients with complicated thoracic aortic dissection etc. Therefore, MHLW has called for reminding healthcare professionals of the above alert by adding following content in the "WARNING" section of the package insert regarding the use of this product in patients who may have complicated thoracic aortic dissection or thoracic aortic aneurysm.

《**PRECAUTIONS** (only related descriptions extracted: underlined parts are additions) 》

[Warning]

WARNING

(1) Cases of death from cerebral haemorrhage have been reported in patients administered with this product. Careful attention should be given to the "WARNING", "CONTRAINDICATIONS" and "PRECAUTIONS" etc. sections and administration should be limited to patients who are considered appropriate for treatment with this drug. The patients should be closely monitored avoiding the emergence of haemorrhagic adverse events such as haemorrhage intracranial associated with administration of this product.

(2) Administration of this product in patients with acute ischemic cerebrovascular disorder increases a risk of serious haemorrhage intracranial. This product should be administered only in situations that meet following criteria.

1) Medical institutions are equipped with SCU, ICU, or equivalents where computerized tomography (CT) and nuclear magnetic resonance imaging (MRI) can be used as needed.

2) Medical institutions are equipped with facilities and a system where sufficient measures can be taken in the event of emergencies such as when haemorrhage intracranial occurs.
3) This product should be used by physicians who have sufficient experience in diagnosis and treatment of ischemic cerebrovascular disorder and diagnostic imaging such as CT.

(3) Cases of aggravation of thoracic aortic dissection or development of thoracic aortic aneurysm rupture leading to death have been reported in patients with acute ischemic cerebrovascular disorder following administration of this product. Healthcare providers should be encouraged to carefully consider the indication when administering this product to patients with possible complicated thoracic aortic dissection or thoracic aortic aneurysm rupture, as suggested by incident chest pain or back pain or chest X-ray findings revealing a widened mediastinum.

[Contraindications]

●**Acute ischemic cerebrovascular disorder**
- Patients who are haemorrhaging (haemorrhage intracranial, gastrointestinal haemorrhage, haemorrhage urinary tract, retroperitoneal haemorrhage, haemoptysis)
- Patients with a high risk of haemorrhage [haemorrhage may be induced.]

[Important Precautions]

●**Acute ischemic cerebrovascular disorder**
- The risk of cerebral haemorrhage is increased following administration of this product. This product should be administered at institutions equipped with SCU, ICU, or an equivalent system. Patients treated with this product should be closely monitored.
- A skull computerized tomography (CT) and nuclear magnetic resonance imaging (MRI) should be performed before administration of this product. If haemorrhage is found, this product should not be administered.
- It has been reported that the use of this product in patients with high blood pressure and blood sugar levels or in patients with low platelet count increases the risk of cerebral haemorrhage. Extreme caution should be exercised when administering this product to such patients. [See the "CONTRAINDICATIONS" section.]
- During administration and within 24 hours after administration of this product, the state of consciousness and neurological symptoms should be frequently monitored. Caution should be exercised against sudden aggravation of these symptoms. If sudden aggravation of the state of consciousness or neurological symptoms is found, diagnostic imaging such as CT should be performed to identify the presence or absence of cerebral haemorrhage.
- Serious haemorrhage may occur. It should be ensured that haemorrhage is detected at an early stage and frequent blood tests including blood coagulation tests should be conducted.

[Adverse Reactions (clinically significant adverse reactions)]

- Serious haemorrhage such as cerebral haemorrhage, gastrointestinal haemorrhage, pulmonary haemorrhage and retroperitoneal haemorrhage may occur. Patients should be closely monitored while receiving this product. If these symptoms occur, administration should be discontinued and appropriate measures should be taken.
  Caution should be exercised since increased haemorrhage may lead to haemorrhagic shock.
- Haemorrhagic cerebral infarction may occur. Patients administered with this product should be closely monitored. If such symptom occurs, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse drug reaction cases between October 2005 (additional indication for acute ischemic cerebrovascular disorder) and May 31, 2007 (events for which a causality to the drug could not be denied)

- Aggravation of thoracic aortic aneurysm, thoracic aortic aneurysm rupture: 8 cases (8 deaths)

The number of patients treated with Alteplase for a year estimated by MAH (Marketing Authorisation Holder): approximately 6600 (October 2005 to May 2007)

Marketed in Japan: May 1991 (additional indication for acute ischemic cerebrovascular disorder: October 2005)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Cerebral infarction (hypertension, pulmonary fibrosis)	25 mg (0.5 mg/kg) Once	**Aggravation of aortic dissection** Cerebral infarction occurred. 1 hour and 55 minutes after onset: CT test was performed. No early CT sign, no haemorrhage, no oedema were found. Level of consciousness disturbed: JCS2 2 hours and 20 minutes after onset: NIHSS18. 2 hours and 40 minutes after onset: Blood pressure was 164/74 mmHg before administration of this product (in supine position). Intravenous administration of this drug was initiated. From onset until this point, the patient did not complain of chest symptoms. 3 hours and 5 minutes after onset: The patient complained chest strangled feeling of. ECG was recorded. 3 hours and 10 minutes after onset: Depressed level of consciousness and blood pressure decreased were noted. Nicardipine hydrochloride was discontinued, and dopamine hydrochloride was initiated. 3 hours and 20 minutes after onset: Administration of this drug was discontinued. Possible aortic dissection was suggested on thoracoabdominal CT. 4 hours and 7 minutes after onset: Blood pressure decreased and respiratory arrest were noted. Respiratory assistance was started. 4 hours and 15 minutes after onset: Cardiac massage was initiated. 4 hours and 22 minutes after onset: Pericardiocentesis and drainage were initiated. 5 hours and 42 minutes after onset: The patient died. Cause of death: Aortic dissection, cardiac tamponade
	Concomitant medications: nicardipine hydrochloride			

Clinical Laboratory Values

	2 hours and 40 minutes after onset	3 hours and 5 minutes after onset	3 hours and 14 minutes after onset
Systolic blood pressure (mmHg)	164	104	68
Diastolic blood pressure (mmHg)	74	94	42
Pulse rate (/minute)	111	--	117
Body temperature (°C)	35.0	--	--

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Cerebral infarction (thoracic dissecting aortic aneurysm)	6.9 mg (0.17 mg/kg) Once	**Aortic aneurysm rupture** Cerebral infarction occurred. 50 minutes after onset: CT and MRI tests were performed. No early CT sign, no haemorrhage, and no oedema were found. Responsible focus: Perforators and cortical branches of right internal carotid artery Size of infarction: Medium/large (actual measurement exceeds 1.5 cm) Level of consciousness disturbed: JCS2 1 hour and 30 minutes after onset: NIHSS12. Measurement time unknown: Blood pressure was 134/73 mmHg before administration of this drug (in supine position). 1 hour and 42 minutes after onset: Intravenous administration of this drug was started (time required for administration: 12 minutes). 1 hour and 55 minutes after onset: The patient's conditions became aggravated 13 minutes after administration (blood pressure was 95/52 mmHg, pulse rate was 68/min.). Administration of this drug was discontinued (the total dose was 6.9 mg). 1 hour and 57 minutes after onset: Consciousness disturbed developed 2 minutes after discontinuation, the patient presented with state of shock. 2 hours and 10 minutes after onset: Upon conducting a chest CT test, cardiac tamponade and dissecting aortic aneurysm, thoracic were found. 2 hours and 35 minutes after onset: Since the patient had cardio-respiratory arrest, cardiac massage was carried out. 3 hours and 11 minutes after onset: The patient was confirmed to be dead. Cause of death: Aortic aneurysm rupture
	Concomitant medications: edaravone			

Clinical Laboratory Values

	Before administration	1 hour and 55 minutes after onset	1 hour and 57 minutes after onset	2 hours and 35 minutes after onset
Systolic blood pressure (mmHg)	134	95	50s	0
Diastolic blood pressure (mmHg)	73	52	--	--
Pulse rate (/minute)	--	68	--	--

2 Oxycodone Hydrochloride Hydrate

Brand Name (name of company)	OxyContin Tablets 5 mg, 10 mg, 20 mg, and 40 mg, OxiNorm Powder 0.5% (Shionogi & Co., Ltd.)
Therapeutic Category	Opium alkaloids
Indications	Analgesia for various forms of cancer accompanied by moderate to severe pain

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder: Hepatic function disorder with marked elevations of AST (GOT), ALT (GPT), AI-P levels etc. may occur. Patients should be closely observed and if abnormalities are found, appropriate measures, such as discontinuation of administration, should be taken.

<Reference Information>

The number of reported adverse drug reaction cases in about the last 3 years (April 1, 2004 to May 18, 2007) (events for which a causality to the drug could not be denied)
• Hepatic function disorder: 7 cases (of which 1 had a fatal case)
The number of patients treated with oxycodone hydrochloride hydrate for a year estimated by MAH: approximately 90000 patients (July 2006 to June 2007)
Marketed in Japan in : July 2003

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Cancer pain (residual gastritis, thrombocytopenia, hypocalcaemia, insomnia)	15 mg 1 day ↓ 20 mg 2 days	**Liver disorder** Past history: Acute renal failure On day 1 of administration: Administration of this drug was initiated for pain from reoccurrence in the neck area after operation for oesophageal carcinoma. On day 2 of administration: Nausea considered to be an adverse reaction to this drug was noted, but administration was continued. On day 3 of administration (day of discontinuation): Since the patient complained of physical deconditioning, he was blood-tested and liver disorder was confirmed. Administration of this drug was discontinued immediately. The patient was treated by drip infusion of glycyrrhizin/glycine/cysteine . The patient presented with urination impaired. 2 days after discontinuation: Physical conditions were gradually recovered. 3 days after discontinuation: Improving trends in AST (GOT), ALT (GPT), AI-P and γ-GTP were found in blood test. 4 days after discontinuation: Liver disorder was improved, and recovery of urination impaired was confirmed.
	Concomitant medications: famotidine, aspirin, precipitated calcium carbonate, estazolam			

Clinical Laboratory Values

	5 days before administration	On day 3 of administration (day of discontinuation)	1 day after discontinuation	3 days after discontinuation
AST (GOT) (IU/L)	26	438	372	59
ALT (GPT) (IU/L)	20	383	344	155
AI-P (IU/L)	420	1466	1692	1147
LDH (IU/L)	250	571	464	236
γ-GTP (IU/L)	18	152	158	99
Total bilirubin (mg/dL)	0.21	--	--	--

AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
AI-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Neuralgia of the right thigh [from ileocecal tumour infiltration] (none)	10 mg 5 days	**Hepatic function abnormal** Past history: Hypertension Approx. 3 and half years before administration: The patient underwent resection of ileocecal tumour infiltrating the right external iliac artery and vein. The patient underwent synthetic vascular prosthesis for the right external iliac artery. Enucleation of tumour infiltrating the right femoral nerve was conducted. Thereafter, the patient had neuralgia of the right thigh and pain in the right leg, and received oral administration of loxoprofen sodium. 35 days before administration: The patient had severe pain in these areas, and was administered with morphine sulfate (10 mg) at a different department in this hospital. However, queasy/vomiting, dizziness and light-headed feeling were developed, and the patient discontinued administration on her own after 1 day. On day 1 of administration: The patient was referred to this department from a different department in the same hospital and received a consultation. As treatment for pain, oral administration of 10 mg of this drug and 75 mg/day of diclofenac sodium was initiated. Queasy/vomiting and light-headed feeling developed. On day 2 of administration: Administration of diclofenac sodium was discontinued. On day 5 of administration (day of discontinuation): Pain was improved, but queasy/vomiting and light-headed feeling was intensified, and administration of this drug was discontinued.

				3 days after discontinuation: As treatment for pain, oral administration of 25 mg/day of morphine hydrochloride for internal use was initiated (this day only). Hepatic function disorder developed. 4 days after discontinuation: The patient had pyrexia and strong generalized malaise. Blood test showed hepatic abnormal and the patient was hospitalized. Intravenous administration of glycyrrhizin/glycine/cysteine was initiated. Fentanyl patch (2.5 mg) was applied for treatment of pain. 7 days after discontinuation: The patient recovered from queasy/vomiting and light-headed feeling. 13 days after discontinuation: Improvement in hepatic functions was confirmed. The patient was discharged from the hospital.
	Concomitant medications: diclofenac sodium, amlodipine besilate			

Clinical Laboratory Values

	On day 1 of administration	4 days after discontinuation	10 days after discontinuation
AST (GOT) (IU/L)	20	762	17
ALT (GPT) (IU/L)	16	702	51
AI-P (IU/L)	340	1274	552
LDH (IU/L)	180	957	189
γ-GTP (IU/L)	91	751	301
Total bilirubin (mg/dL)	0.40	1.45	0.48

AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
AI-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase

3 Meropenem Trihydrate

Brand Name (name of company)	Meropen Intravenous Drip Infusion 0.25 g and 0.5 g (Dainippon Sumitomo Pharma Co., Ltd.)
Therapeutic Category	Acting mainly on gram-positive and gram-negative bacteria
Indications	<Susceptible strains> Meropenem susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *S.pneumoniae, Enterococcus sp., N.meningitidis, M.(B.)catarrhalis, E.coli, Citrobacter* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Providencia* sp., *H.influenzae, Pseudomonas, P.aeruginosa, B.cepacia, Bacteroides* sp. *and Prevotella* sp. <Indications> Septicemia, deep-seated skin infection, lymphangitis/lymphadenitis, secondary infection in traumatic wound, burn wound or operative wound, periproctic abscess, osteomyelitis, arthritis, tonsillitis (including peritonsillar abscess), pneumonia, lung abscess, pyothorax, secondary infection in chronic respiratory disease, complicated cystitis, pyelonephritis, peritonitis, cholecystitis, cholangitis, liver abscess, intrauterine infection, uterine adnexitis, parametritis, purulent meningitis, endophthalmitis (including panophthalmitis), Otitis media, sinusitis, phlegmon around the jaw and gnathitis.

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant, hepatic function disorder, jaundice: Serious hepatitis such as hepatitis fulminant, hepatic function disorder and jaundice may occur. Patients should be carefully monitored through periodic clinical and laboratory tests. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse drug reaction cases in about the last 3 years (April 1, 2004 to May 9, 2007) (events for which a causality to the drug could not be denied)
• Hepatitis fulminant: 3 cases (of which 1 had a fatal case)
The number of patients treated with meropenem ttrihydrate for a year estimated by MAH: approximately 600,000 patients (fiscal year 2006)
Marketed in Japan: September 1995

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Pyrexia, cellulitis (pruritus cutaneous associated with dialysis, diabetes mellitus, diabetic renal failure, myocardial infarction)	1 g 2 days	**Hepatitis fulminant** The patient was on dialysis for diabetes mellitus and diabetic renal failure. The patients had acute myocardial infarction, and he repeated changing hospitals. Approx. 3 months before administration: The patient presented with systemic itching. 2 days before administration: The Patient was transferred from Hospital A to Hospital B for treatment of itching. 1 day before administration: Inflammatory reaction in ulcer on the dorsum in the left foot was found, drip infusion of 1 g of cefpirome sulfate was started. As treatment for itching, 10 mg of tandospirone citrate was orally administered 3 times per day, in the morning, noon and afternoon. State of unrest was observed in the nighttime; according to family members, state of unrest was observed each time the patient was transferred to a different hospital. On day 1 of administration: Pyrexia in the 38°C range was observed, and blood pressure decreased to the 80 mmHg range in the nighttime. Blood pressure recovered to 120 mmHg range through leg elevation. Antibiotics were changed from cefpirome sulfate to meropenem trihydrate. Depressed level of consciousness was noted in the nighttime. The patient was diagnosed with a hypoglycaemic attack by measuring blood sugar level. Although level of consciousness improved through glucose injections, the same symptoms were observed 3 times in total. Administration of tandospirone citrate was terminated. On day 2 of administration (day of discontinuation): Hepatic function disorder was confirmed in blood test in the morning. Upon conducting a detailed examination, the patient was diagnosed with hepatitis fulminant, and he was transferred to ICU. The patient had hepatic coma stage II. (development of hepatitis fulminant) Thereafter, plasma exchange was conducted a total of 6 times. Despite treatment with steroid pulse therapy, ciclosporin, etc., liver synthetic capacity did not improve, and DIC, pneumonia, etc., concomitantly occurred. Administration of meropenem trihydrate was terminated. 21 days after discontinuation: Due to sudden change during dialysis, the patient died. Autopsy findings: None
	Concomitant medications: tandospirone citrate, cefpirome sulfate, sulindac, precipitated calcium carbonate, aspirin, lafutidine, propranolol hydrochloride, rebamipide, tocopherol nicotinate, candesartan cilexetil, calcium polystyrene sulfonate, insulin human (Genetical recombination), cyproheptadine hydrochloride, nitroglycerin difluprednate, crotamiton, alprostadil alfadex, povidone-iodine			

Clinical Laboratory Values

	1 day before adminis-tration	On day 2 of administration (day of discontinuation)			1 day after discontinuation		2 days after discon-tinuation	6 days after discon-tinuation	11 days after discon-tinuation	17 days after discon-tinuation	21 days after discon-tinuation
AST (GOT) (IU/L)	11	5774	7857	9053	5397	1214	1160	--	--	47	55
ALT (GPT) (IU/L)	10	2493	3007	3433	3130	691	1103	--	--	38	67
AI-P (IU/L)	--	867	688	--	960	--	589	--	--	473	712
LDH (IU/L)	268	12130	--	--	--	--	--	--	--	—	—
γ-GTP (IU/L)	26	56	--	--	--	--	--	--	--	—	—
Total bilirubin (mg/dL)	0.4	2.1	2.8	--	3.0	2.5	5.3	--	--	14.4	23.8
Cholinesterase (IU/L)	--	--	123	--	133	--	279	--	--	179	105
CRP (mg/dL)	7.09	14.44	11.96	--	12.33	--	6.24	--	--	4.35	1.90
Prothrombin time (%)	--	--	--	24.0	20.0	68.0	38.0	--	--	51.0	21.4
APTT (seconds)	--	--	--	58.4	97.9	--	114.8	--	--	59.6	92.2
ATIII (%)	--	--	--	--	48	--	71	--	--	55	50
Ammonia (μg/dL)	--	--	--	--	51.7	30.9	22.1	--	--	71.1	55.0
HBs-Ag	--	--	--	--	--	--	--	0.04	--	—	—
HBs-Ab	--	--	--	--	--	--	--	64.88	--	—	—
HCV-Ab	--	--	--	--	--	--	--	0.13	--	—	—
Platelet count ($\times 10^4/mm^3$)	32.4	26.7	22.8	21.6	12.4	10.0	11.8	--	--	2.7	7.4
WBC count ($/mm^3$)	13460	34630	31160	28650	18830	19630	19050	--	--	36690	34480
Albumin (g/dL)	0.31	--	--	--	--	--	--	--	--	—	—
Degree of coma	Unrest in night time	Hepatic coma stage II			--	--	--	--	--	--	--
Abdominal (hepatic) CT findings	--	Decrease in concentration of hepatic parenchyma			--	--	--	--	Liver atrophied, atrophy of right lobe progressed	--	--

AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
AI-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
CRP: C-Reactive Protein
APTT: Activated Partial Thromboplastin Time
ATIII: Antithrombin III
HBs-Ag: Hepatitis Virus Bs Antigen
HBs-Ab: Hepatitis Virus Bs Antibody
HCV-Ab: Hepatitis C Virus Antibody
WBC: White Blood Cell

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 80s	Pneumonia (lung cancer)	1 g 17 days ↓ (no treatment for 20 days) ↓ 1 g 12 days	**Hepatitis fulminant** The patient had terminal lung cancer and had undergone the following clinical course. On day 1 of administration: The patient received consultation at Hospital B due to pneumonia. By measuring number of tubercle bacillus in sputum, Gaffky scale no. 4 was confirmed and he was transferred from Hospital B to Hospital A due to suspicion of tuberculosis. The patient received treatment at Hospital A (until 12th day of readministration of meropenem trihydrate (day of discontinuation of readministration)). Tuberculosis treatment with isoniazid (INH), rifampicin (RFP) and ethambutol (EB) was initiated. Pneumonia was also suspected, and administration of meropenem trihydrate (0.5 g x 2 times) was initiated. On day 14 of administration: Liver disorder was confirmed. AST (GOT) 267 IU/L, ALT (GPT) 88 IU/L. INH,RFP and EB were considered to be associated with this event. On day 17 of administration (day of discontinuation): CRP was 38.95 mg/dL at hospitalization, but then decreased to 1.87 mg/dL. Since pneumonia was improved, administration of this drug was discontinued. AST (GOT) 582 IU/L, ALT (GPT) 331 IU/L. 3 days after discontinuation: Due to liver disorder, INH, RFP and EB were discontinued. Hepatic function test values improved rapidly after discontinuing administration of antituberculosis drug. 8 days after discontinuation: After incubation, tubercle bacillus mycobacteria were not detected and only atypical acid fast bacterium was confirmed. Tuberculosis was excluded. As a result, the patient was transferred from the tuberculosis ward to the general ward. In the general ward, only management of systemic conditions of the patient was conducted. Lung cancer markers were high, and the patient was in terminal state of lung cancer. Dementia was severe. The patient continued sleeping in the daytime, and delirium was observed in the night. Communication was nearly impossible. The patient ate 20 to 30% of meals, and there were no changes during the clinical course. 11 days after discontinuation: CRP decreased to 0.48 mg/dL. 21 days after discontinuation: (day that administration was restarted) Since CRP increased again to 7.18 mg/dL, and pyrexia was found, pneumonia was suspected and administration of this drug (0.5 g × 2 times) was reinitiated.

				After initiating administration, there were no particular changes in his conditions, and there were also no abnormalities. Since a transfer to Hospital B was planned after reinitiating administration of this drug, a blood test was not conducted. On 12 day of readministration: (day of discontinuation of readministration) The patient was transferred to Hospital B (for treatment of lung cancer and dementia. Tuberculosis was negative, and pneumonia was cured.) Hepatitis fulminant was suspected in a blood test conducted when the patient was transferred to Hospital B (day of onset was unknown). Administration of this drug was discontinued. On admission to Hospital B, symptoms of jaundice etc. were not noted. AST (GOT) 1571 IU/L, ALT (GPT) 996 IU/L, platelet count $4.6 \times 10^4/mm^3$. Upon making inquiries to Hospital A, serious liver disorder was suspected. 1 day after discontinuation of readministration: AST (GOT) 1833 IU/L, ALT (GPT) 1120 IU/L, platelet count $3.4 \times 10^4/mm^3$. Administration of glycyrrhizin/glycine/cysteine was initiated. 2 days after discontinuation of readministration: AST (GOT) 1187 IU/L, ALT (GPT) 953 IU/L, platelet count $3.4 \times 10^4/mm^3$, FDP 22.7 μg/dL. DIC (disseminated intravascular coagulation) was suspected, and nafamostat mesilate was initiated. 3 days after discontinuation of readministration: Platelets count $2.1 \times 10^4/mm^3$. ATIII (antithrombin III) was also administered. G-I (glucagons-insulin) therapy was initiated. Pulse therapy using 500 mg of methylprednisolone sodium succinate was performed (until next day). 5 days after discontinuation of readministration: AST (GOT) 353 IU/L, ALT (GPT) 563 IU/L, platelet count $1.7 \times 10^4/mm^3$. The patient received transfusion of 5 units of concentrated human platelets. 8 days after discontinuation of readministration Systolic blood pressure decreased to 60 mmHg range. Haemoglobin 5.4 g/dL, platelet count $3.2 \times 10^4/mm^3$, albumin 1.3 g/dL, AST (GOT) 240 IU/L, ALT (GPT) 351 IU/L. Dopamine hydrochloride, noradrenaline, FFP (fresh frozen human plasma), MAP (concentrated human red blood cells) was initiated. 9 days after discontinuation of readministration: The patient died. Autopsy findings: None
	Concomitant medications: isoniazid, rifampicin, ethambutol, amino acid/sugar/electrolytes, famotidine, haloperidol, biperiden hydrochloride, risperidone, lactomin, thiamine monophosphate disulfide			

Clinical Laboratory Values

	On day 2 of admin.	On day 4 of admin.	On day 11 of admin.	On day 14 of admin.	On day 17 of admin. (day of discont-inuation)	4 days after discont-inuation	11 days after discont-inuation	21 days after discont-inuation (day that adminis-tration was restarted)	12th day of read-ministra-tion (day of discont-inuation)	1 day after discont-inuation of read-ministra-tion	2 days after discont-inuation of read-ministra-tion	3 days after disconti nuation of read-ministra-tion	5 days after disconti nuation of read-ministra-tion	7 days after disconti nuation of read-ministra-tion	8 days after disconti nuation of read-ministra-tion
AST (GOT) (IU/L)	55	35	28	267	582	85	41	66	1571	1833	1187	875	353	161	240
ALT (GPT) (IU/L)	29	30	19	88	331	173	69	51	996	1120	953	839	563	402	351
AI-P (IU/L)	208	222	255	323	569	429	308	275	1652	1647	1474	1378	1114	913	640
γ-GTP (IU/L)	27	--	--	--	--	--	--	--	158	154	144	133	111	104	90
LDH (IU/L)	300	271	226	402	293	206	196	289	804	820	775	697	665	701	551
Total bilirubin (mg/dL)	1.30	0.92	0.85	0.88	0.71	0.80	0.44	0.60	2.3	2.3	2.4	2.1	1.4	1.3	1.2
Cholinesterase (IU/L)	60	--	--	--	--	--	--	--	106	97	93	88	81	81	55
LAP (IU/L)	--	--	--	--	--	--	--	--	--	--	128	123	--	--	--
Ammonia (μg/dL)	--	--	--	--	--	--	--	--	46	--	--	--	21	12	--
Prothrombin time (%)	70.4	--	59.3	--	--	--	--	--	43.8	41.3	42.4	45.7	64.2	--	--
APTT (seconds)	46.1	--	41.7	--	--	--	--	--	40.5	43.0	37.7	49.2	42.4	--	--
Albumin (g/dL)	2.5	2.1	1.9	1.8	1.9	2.1	2.2	2.3	2.3	2.1	2.0	1.8	1.8	1.8	1.3
Platelet count ($\times 10^4/mm^3$)	16.9	12.7	33.0	33.3	25.3	19.3	29.8	13.8	4.6	3.4	3.4	2.1	1.7	6.7	3.2
WBC ($/mm^3$)	18000	9100	6100	8700	2900	4200	4900	6600	6930	4580	4210	3490	8330	5260	2170
HBs-Ag	(–)	--	--	--	--	--	--	--	(–)	--	--	--	--	--	--
HCV-Ab	(–)	--	--	--	--	--	--	--	(–)	--	--	--	--	--	--
CRP (mg/dL)	38.95	16.96	6.19	4.52	1.87	0.79	0.48	7.18	0.76	0.65	0.60	0.77	0.27	1.89	5.92

AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
AI-P: Alkaline Phosphatase
γ-GTP: γ-Glutamyltranspeptidase
LDH: Lactate Dehydrogenase
LAP: Leucine Aminopeptidase
APTT: Activated Partial Thromboplastin Time
WBC: White Blood Cell
HBs-Ag: Hepatitis Virus Bs Antigen
HCV-Ab: Hepatitis C Virus Antibody
CRP: C-Reactive Protein

2

Revision of PRECAUTIONS

(No. 189)

This section presents details of revisions of "PRECAUTIONS" in package inserts and brand names of drugs that have been revised according to the Notifications dated July 6, 2007 (excluding those presented in "1 Important Safety Information" of this Bulletin).

< Hypnotics and sedatives, anxiolytics>

1 Amobarbital, Barbital, Phenobarbital (oral dosage form), Bromovalerylurea, Pentobarbital Calcium, Chloral Hydrate (oral dosage form)

[Brand Name]

Isomytal (Nippon Shinyaku Co., Ltd.)
Barbital "Ebisu" (Ebisu Pharmaceutical Co.), Barbital "Hoei" (Merck Pharma Ltd.)
Phenobal Powder, Phenobal Powder 10%, Phenobal Tablets 30 mg, Phenobal Elixir 0.4% (Fujinaga Pharm Co., Ltd.) and others
Brovarin (Nippon Shinyaku Co., Ltd.) and others
Ravona Tablets (Tanabe Seiyaku Co., Ltd.)
Chloral Hydrate "Hoei" (Merck Pharma Ltd.

[Precautions of Dosage and Administration]

Patients with insomnia should be instructed to take this product immediately before bedtime. Patients should be instructed not to take this product if they may have to wake up temporarily for working etc. after taking this product at bedtime.

< Hypnotics and sedatives, anxiolytics>

2 Estazolam, Nitrazepam, Nimetazepam, Haloxazolam, Flurazepam Hydrochloride, Lormetazepam

[Brand Name]

Eurodin Powder 1%, Eurodin 1 mg. and 2 mg. Tablets (Takeda Pharmaceutical Company Limited) and others
Nelbon Powder 1%, Nelbon Tablets 5 mg and 10 mg (Daiichi-Sankyo Co., Ltd.), Benzalin Fine Granules 1%, Benzalin Tablets 5 and 10 (Shionogi & Co., Ltd.) and others
Erimin Tablets 3 and 5 (Dainippon Sumitomo Pharma Co., Ltd.)
Somelin Fine Granules, Somelin Tablets 5 mg and 10 mg (Daiichi-Sankyo Co., Ltd.)
Benozil Capsules 10 and 15 (Kyowa Hakko Kogyo Co., Ltd.) and others
Evamyl Tablets 1.0 (Bayer Yakuhin, Ltd.), Loramet Tablets 1.0 (Wyeth K.K.)

[Precautions of Dosage and Administration]

Patients with insomnia should be instructed to take this product immediately before bedtime. Patients should be instructed not to take this product if they may have to wake up temporarily for working etc. after taking this product at bedtime.

[Serious Adverse Reactions (similar drugs)]

Transient anterograde amnesia, twilight state: Transient anterograde amnesia and twilight state may occur following administration of similar drugs (other therapeutic agents for insomnia). This product should be administered with caution, such as initiating treatment with low dose. There have been reports of driving, eating etc. while not fully awaken and without remembering these activities in patients taking similar drugs. If any abnormalities are observed, administration of this product should be discontinued.

< Hypnotics and sedatives, anxiolytics>

3 Quazepam, Flunitrazepam (oral dosage form), Brotizolam, Rilmazafone Hydrochloride

[Brand Name]

Doral Tablets 15 and 20 (Hisamitsu Pharmaceutical Co., Inc.)
Silece Tablets 1 mg and 2 mg (Eisai Co., Ltd.), Rohypnol Tablets 1 and 2 (Chugai Pharmaceutical Co., Ltd.) and others
Lendormin Tablets 0.25 mg, Lendormin D Tablets 0.25 mg (Nippon Boehringer Ingelheim Co., Ltd.) and others
Rhythmy Tablets 1 mg and 2 mg (Shionogi & Co., Ltd.)

[Precautions of Dosage and Administration]

Patients with insomnia should be advised to take this product immediately before bedtime. Patients should be instructed not to take this product if they may have to wake up temporarily for working etc. after taking this product at bedtime.

[Adverse Reactions (clinically significant adverse reactions)]

Transient anterograde amnesia, twilight state: Transient anterograde amnesia and twilight state may occur following administration of this product. This product should be administered with caution, such as initiating treatment with low dose. There have been reports of driving, eating etc. while not fully awaken and without remembering these activities in patients taking this product. If any abnormal findings are observed, administration of this product should be discontinued.

< Expectorants>

4 Ambroxol Hydrochloride

[Brand Name]

Mucosolvan Tablet, Mucosolvan L Capsule, Mucosolvan Syrup, Mucosolvan DS 1.5% for Pediatric, Mucosolvan DS 3%, Mucosolvan Solution (Teijin Pharma Limited) and others

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome):
Oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur. Patients should be closely monitored, and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

< Respiratory organ agents-Miscellaneous>

5 Fluticasone Propionate (inhalant)

[Brand Name] Flutide 50 Air and 100 Air, Flutide 50 Diskus, 100 Diskus, and 200 Diskus, Flutide 50 Rotadisk, 100 Rotadisk, and 200 Rotadisk (GlaxoSmithKline K.K.)

[Precautions of Dosage and Administration] If relief of symptoms is noted, patients should be administered with this product at the minimum therapeutic dose.

[Important Precautions] If aggravation of asthmatic symptoms accompanying infection is noted, increasing the dose of steroid therapy and treatment of infections should be considered.

< Digestive organ agents-Miscellaneous>

6 Infliximab (Genetical recombination)

[Brand Name] Remicade for I.V. Infusion 100 (Tanabe Seiyaku Co., Ltd.)

[Important Precautions] It has been reported that use of TNF inhibitors, including this product have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus.

When this product is administered to hepatitis B carrier patients, healthcare providers should be alerted to the development of signs and symptoms of reactivation of the hepatitis B virus by monitoring liver function tests and hepatitis viral markers. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system.

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder:** Hepatic function disorder with significant elevations of AST(GOT), ALT(GPT), γ-GTP levels etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this product should be discontinued and appropriate measures should be taken.

7 <Miscellaneous metabolism agents >

Etanercept (Genetical recombination)

[Brand Name] Enbrel 25 mg for s.c. Injection (Wyeth K.K.)

[Important Precautions] Reactivation of the hepatitis B virus has been reported in hepatitis B virus carrier patients administered with anti-TNF drug products including this product, When this product is administered to Hepatitis B carrier patients, healthcare providers should be alerted to the development of signs and symptoms of reactivation of the hepatitis B virus by monitoring liver function tests and hepatitis viral markers. The reactivation has been most commonly reported in patients who have received a concomitant treatment with this product and other immunosuppressive agents.

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder:** Hepatic function disorder with elevations of AST(GOT) or ALT(GPT) etc may occur. Patients should be closely monitored, and if abnormalities are observed, administration of this product should be discontinued and appropriate measures should be taken.

8 < Antivirals, Biological preparations-Miscellaneous>

Ribavirin (tablet), Peginterferon Alfa-2a (Genetical recombination)

[Brand Name] Copegus Tablet 200 mg (Chugai Pharmaceutical Co., Ltd.)
Pegasys s.c. 90 μg and 180 μg (Chugai Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythema multiforme:** Skin disorders such as oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythema multiforme etc. may occur. Patients should be closely monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

3

List of products subject to Early Post-marketing Phase Vigilance

(As of August 1, 2007)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Rurioctocog Alfa (Genetical recombination) Advate Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method for Injection 250, 500, and 1000	Baxter Limited	February 22, 2007
Follitropin Beta (Genetical recombination) Follistim Inj. 50 and 75[*1]	Nippon Organon K.K.	March 16, 2007
Peginterferon Alfa-2a (Genetical recombination) Pegasys s.c. 90 μg and 180 μg[*2]	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Ribavirin Copegus Tablet 200 mg	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Modafinil Modiodal Tablets 100 mg	Alfresa Pharma Corporation	March 28, 2007
Levonorgestrel-releasing Intrauterine Contraceptive System Mirena 52 mg	Bayer Yakuhin, Ltd.	April 16, 2007
Valaciclovir Hydrochloride Valtrex Granules 50%[*3]	GlaxoSmithKline K.K.	April 18, 2007
Entacapone Comtan Tablets 100 mg	Novartis Pharma K.K.	April 19, 2007
Pegvisomant (Genetical recombination) Somavert for s. c. Injection 10 mg, 15 mg, and 20 mg	Pfizer Japan Inc.	June 5, 2007
Salmeterol Xinafoate/Fluticasone Propionate Adoair 100 Diskus, 250 Diskus, and 500 Diskus	GlaxoSmithKline K.K.	June 8, 2007
Ciclesonide Alvesco 50 μg Inhaler 112 puffs, 100 μg Inhaler 112 puffs, and 200 μg Inhaler 56 puffs	Teijin Pharma Limited	June 8, 2007
Fondaparinux Sodium Arixtra Injection 1.5 mg and 2.5 mg	GlaxoSmithKline K.K.	June 8, 2007
Imidafenacin Uritos Tablets 0.1 mg	Kyorin Pharmaceutical Co., Ltd.	June 11, 2007
Imidafenacin Staybla Tablets 0.1 mg	Ono Pharmaceutical Co., Ltd.	June 11, 2007
Ezetimibe Zetia Tablets 10 mg	Schering-Plough K.K.	June 11, 2007

Bevacizumab (Genetical recombination) Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL	Chugai Pharmaceutical Co., Ltd.	June 11, 2007
Celecoxib Celecox Tablets 100 mg and 200 mg	Astellas Pharma Inc.	June 12, 2007
Sodium Risedronate Hydrate Actonel Tab. 17.5 mg	Ajinomoto Co., Inc.	June 15, 2007
Sodium Risedronate Hydrate Benet Tablets 17.5 mg	Takeda Pharmaceutical Company Limited	June 15, 2007
Monobasic Sodium Phosphate Monohydrate/Dibasic Sodium Phosphate Anhydrous Visiclear Tablets	Zeria Pharmaceutical Co., Ltd.	June 15, 2007
Amiodarone Hydrochloride Ancaron Injection 150	Sanofi-Aventis K.K.	June 22, 2007
Darbepoetin Alfa (Genetical recombination) Nesp Injection Syringe 10 μg syringe, 15 μg syringe, 20 μg syringe, 30 μg syringe, 40 μg syringe, 60 μg syringe, and 120 μg syringe	Kirin Pharma Company, Limited	July 9, 2007
Fludarabine Phosphate Fludara Tab. 10 mg	Bayer Yakuhin, Ltd.	July 12, 2007

*1: Additional indications for "the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders"

*2: Additional indications for "improvement of viraemia in concomitant use of ribavirin in chronic hepatitis C (1) or (2): (1) serogroup 1 (patients for genotype I (1a) or II (1b) with high blood HCV-RNA load, or (2) patients who failed interferon monotherapy or who developed reactivation of the disease following interferon monotherapy"

*3: Additional indications for "varicella"