Pharmaceuticals and Medical Devices Safety Information

No. 230 November 2006

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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 information 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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Pharmaceuticals and Medical Devices Safety Information

No. 230 November 2006

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

[Outline of Information]

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

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

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

1

Manuals for Management of Individual Serious Adverse Drug Reactions

1. Introduction

Ministry of Health, Labour and Welfare (MHLW) has been preparing "Manuals for Management of Individual Serious Adverse Drug Reactions" (hereinafter referred to as "the Manuals") with cooperation of experts etc. from relevant medical societies since FY2005 as a 4-year "Project of Comprehensive Measures for Serious Adverse Reactions". The first series of manuals of adverse drug reactions, including "Stevens-Johnson syndrome" and "interstitial pneumonia", have been finalized and are available on the MHLW website (http://www.mhlw.go.jp/) and the Pharmaceutical and Medical Devices Information website (http://www.info.pmda.go.jp/). This section presents the objective and process of this project, as well as information about the Manuals.

2. Project of Comprehensive Measures for Serious Adverse Reactions

(1) Objective

The current safety measures are drug-oriented and mainly "alert-release" and "post-event response" types, i.e., information of adverse reactions were collected and evaluated for each drug and notified to physicians and healthcare providers as revisions of the package insert etc. However, these types of measures may delay recognition of adverse reactions and cause serious conditions due to the following reasons.

① Adverse reactions may occur in the organs in which the attending physicians are not specialized.

② Incidence of serious adverse reactions is generally low and physicians and healthcare providers may have a little experience with such events. Therefore, in some cases, detection of adverse reactions may delay, leading to the increased severity.

The objective of this project is to modernize safety measures that "predict" and "prevent" adverse drug reactions by preparing adverse-reaction oriented, not drug-oriented, safety measures in addition to current safety measures and by promoting researches which elucidate mechanism of adverse reactions.

(2) Process

This project will proceed in the following three steps starting in FY2005.

1st step: "Preparation for early recognition of and prompt response to adverse reactions"

We will promote early recognition of and prompt response to adverse reactions in clinical practice by preparing and publishing manuals. The manuals summarize comprehensively information of adverse reactions that are considered to be highly necessary based on the severity of the adverse reactions, including recognition and treatment methods useful for patients and clinicians such as physicians and pharmacists. We plan to complete and publish those manuals in four years.

2nd step: "Preparation for prediction of adverse reactions"

The Manuals will be revised based on the findings in high-risk patient group, which are obtained by collecting and analyzing adverse reaction cases.

3rd step: "Preparation for prevention of adverse reactions"

Investigation of risk factors and researches on mechanism of adverse reactions should be promoted. The drug use in high-risk patient group should be prevented in clinical practice, and in pharmaceutical industries, new drugs that cause less adverse reactions should be developed.

3. Information about the Manuals

Preparation of Manuals for Management of Individual Serious Adverse Drug Reactions was discussed in the first Review Meeting on Comprehensive Measures for Serious Adverse Reactions (Chairman: Kazunori Matsumoto, Professor at International University of Health and Welfare) on July 19, 2005. The adverse drug reactions for which Manuals should be prepared (**Table 1**) and items described in the Manuals (**Table 2**) were decided.

The important points regarding the items include ① to clearly summarize the keys to early recognition of and prompt response to adverse reactions for both patients and healthcare providers, ② to describe the distinction and treatment methods for adverse drug reactions, bearing in mind that healthcare providers may have a little experience with such cases, and ③ to present typical cases.

MHLW has been drafting Manuals based on the discussion results with cooperation of relevant medical societies. In the second Review Meeting on Comprehensive Measures for Serious Adverse Reactions on October 19, 2006, the evaluation and discussion were completed for Stevens-Johnson syndrome, toxic epidermal necrosis, interstitial pneumonia, acute lung injury, acute respiratory distress syndrome, asthmatic attack due to nonsteroidal anti-inflammatory drug, drug-induced Parkinsonism, rhabdomyolysis, leukoencephalopathy, and pseudoaldosteronism.

Table 1. List of subject adverse drug reactions included in the Manuals

Field	Names of cooperating society	Subject adverse reaction
Dermatologicals	The Japanese Dermatological Association	Stevens-Johnson syndrome*
		Toxic epidermal necrosis*
		Drug-induced hypersensitivity syndrome
Hepatic	The Japan Society of Hepatology	Drug-induced liver disorder
Renal	The Japanese Society of Nephrology	Acute renal failure
		Nephritis interstitial
Blood	The Japanese Society of Hematology	Agranulocytosis
		Aplastic anaemia
		Thrombocytopenia
		Anaemia
		Thrombosis
		Disseminated intravascular coagulation
Respiratory system	The Japanese Respiratory Society	Interstitial pneumonia*
		Asthmatic attack due to nonsteroidal anti-inflammatory drug*
		Acute lung injury/Acute respiratory distress syndrome*
Alimentary tract	The Japanese Society of Gastroenterology	Ileus paralytic
		Peptic ulcer
		Pseudomembranous colitis
Cardiovascular system	The Japanese Circulation Society	Ventricular tachycardia
		Cardiac failure congestive
		Cardiac function disturbance
Nervous and musculo-skeletal system	The Japanese Society of Neurology	Drug-induced Parkinsonism*
		Rhabdomyolysis*
		Leukoencephalopathy*
		Peripheral nerve disorder

Psychiatric	The Japanese Society of Clinical Neuropsychopharmacology	Neuroleptic malignant syndrome
		Depression
Metabolism and endocrine	The Japan Endocrine Society	Pseudoaldosteronism*
	The Japan Diabetes Society	Hypoglycaemia
Hypersensitivity	The Japanese Society of Allergology	Anaphylaxis
		Urticaria/Angioedema

✳: The second Review Meeting on Comprehensive Measures for Serious adverse reactions selected additional adverse reactions including nephrotic syndrome, pulmonary oedema, and movements involuntary for the conventional fields of renal, respiratory system, and nervous and musculo-skeletal system and metabolism and endocrine systems as well as new fields of sensory organs (e.g., visual disturbance), pancreas (pancreatitis), oral cavity (stomatitis), bones (e.g., osteonecrosis), and urinary organs (e.g., urinary retention).

* The adverse reactions for which the Manuals were published this time.

Table 2. Items described in the Manuals

	Items	Content
1	Name of the adverse reaction	Descriptions of the name including synonyms
For patients		
2	Summary of the adverse reaction The keys to early recognition and prompt response	The keys to early recognition of and prompt response to the adverse reaction for patients and their families
For healthcare providers		
3	The keys to early recognition and prompt response	The points to which healthcare providers should pay attention.
4	Summary of the adverse reaction	Summary of the adverse drug reaction, including symptoms
5	Distinction criteria for the adverse reaction (distinction method)	Summary of criteria for distinction between the adverse reaction and primary or other diseases
6	Diseases that should be distinguished and distinction method	Summary of methods to distinguish between the adverse reaction and other diseases
7	Treatment methods	Treatments that may be performed when the adverse reaction occurs.
8	Case summaries of typical adverse reactions	Case summaries that can serve as a reference of typical adverse reaction
9	Cited literatures/References	A list of cited literatures and relevant materials in the Manual

4. Closing comments

The manuals prepared this time were notified to the prefectural and city governments, the Japan Medical Association, the Japan Pharmaceutical Association, the Japanese Society of Hospital Pharmacists, and other relevant parties and are available on the websites of MHLW and the Pharmaceutical and Medical Devices Information.

Preparation of draft manuals will be continued with cooperation of relevant medical societies and Japanese Society of Hospital Pharmacists. The final manuals will be published after evaluation and discussion in the Review Meeting on Comprehensive Measures for Serious adverse reactions.

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

2

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 issue before previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 228).

1 Amantadine Hydrochloride

Brand Name (name of company)	Atenegine Fine Granules, Atenegine 50 and 100 (Tsuruhara pharmaceutical Co., Ltd.) Amazolon Fine Granules, Amazolon Tablets 50 and 100 (Sawai Pharmaceutical Co., Ltd.) Amantadine HCl Tablets 50 "Nichiiko" (Nichi-iko Pharmaceutical Co., Ltd.) Shikitan (Zensei Pharmaceutical Industries Co., Ltd.) Symmetrel Fine Granules, Symmetrel Tablets 50 mg and 100 mg (Novartis Pharma K.K.) Topharmin Fine Granules, Topharmin Tablets 50 and 100 (Toyo Pharmar Co., Ltd.) Boidan Powder, Boidan Tablets 50 mg and 100 mg (ISEI Co., Inc.) Lusyton Fine Granules, Lusyton Tablets (Tatsumi Kagaku Co., Ltd.) Rotifamin Tablets 50 and 100 (Yaiyo Yakuhin Co., Ltd.)
Therapeutic Category	Antiparkinsonian agents
Indications	○ Improvement of decreased motivation and initiative associated with late effects of cerebral infarction ○ Parkinson syndrome ○ Influenza A virus infection

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

[Contraindications]

Patients with serious renal disorders who require haemodialysis [This drug is excreted in urine mainly as unchanged drug. Accumulation of this drug may cause adverse reactions such as disturbances of consciousness psychiatric symptom, convulsion, and myoclonus. It should be noted that the amount of this drug that can be removed by haemodialysis is limited.]

[Precautions of Dosage and Administration]

This drug is excreted in urine mainly as unchanged drug, resulting in high blood concentrations in patients with function kidney decreased, which may cause adverse reactions such as disturbances of consciousness, psychiatric symptom, convulsion, and myoclonus. Therefore, this drug should be used with caution, such as by extending dosing intervals depending on the level of kidney function.

[Adverse Reactions (clinically significant adverse reactions)]

Disturbances of consciousness (including coma), psychiatric symptoms (e.g. hallucination, delusion, delirium, and confusion), convulsion, and myoclonus: Disturbances of consciousness (including coma), psychiatric symptoms (e.g. hallucination, delusion, delirium, and confusion), convulsion, and myoclonus may occur. Appropriate measures such as tapering-off and discontinuation of treatment should be taken in such cases. Caution should be exercised for patients with function kidney decreased, who are more susceptible to these reactions.

<Reference Information>

Company report
The number of reported adverse reaction cases in about the last 3 years (April 1,

2003 to July 31, 2006) (events for which a causality to the drug could not be denied)
• Myoclonus: 9 cases (no fatal case)
The number of patients treated with Amantadine estimated by MAH (Marketing Autorisation Holder): approximately 0.4 million (FY2005)
Marketed in Japan in: 1975

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	Vascular parkinsonism (chronic renal failure, diabetic nephropathy, and diabetes mellitus)	150 mg 53 days	**Gait disturbance, hallucination, and movements involuntary** Approx. 26 years before administration: The patient had diabetes mellitus and had been treated by a local doctor. Approx. 3 years before administration: The patient developed cerebral infarction and hospitalized to the neurosurgery department at the local hospital. During the follow-up visits after discharge, he had aphasia and dysphagia. Approx. 2 years before administration: Creatinine (Cr) 1.7 mg/dL, proteinuria (3+). Approx. 8 months before administration: Renal failure due to diabetic nephropathy was observed with Cr of 4.7 mg/dL. Approx. 3 months before administration: The renal failure progressed with Cr of 6.3 mg/dL. On day 1 of administration: Amantadine hydrochloride at 150 mg was started for the treatment of symptoms of cerebrovascular Parkinsonism. On day 36 of administration: Gait disturbance, hallucination, and movements involuntary developed. On day 53 of administration (day of discontinuation): The patient had an outpatient visit at our hospital. He was emergently hospitalized with BUN 101 mg/dL, Cr 8.9 mg/dL, and K 7.2 mEq/L. [Physical findings on admission] Body temperature 36.3 C, blood pressure 205/80 mmHg, pulse rate 60 beats/min (regular). The patient had a JCSI-3 level of consciousness. Neurological observations were rigidity of limbs, masked face, and movements involuntary such as pill-rolling tremor. Abasia developed. Tendon reflexes were symmetrical. [Laboratory findings on admission] Normochromic normocytic anaemia was observed with haemoglobin 7.2 g/dL and haematocrit 22.5%.	Company report

				Proteinuria was (3+). Head CT revealed old cerebral infarction lesions in the white matter of the cerebral hemisphere, bilateral basal ganglia, and left thalamus, but no new infarction or haemorrhagic lesions were observed. [Clinical course after admission] Ultrasound revealed the renal atrophy, indicating chronic renal failure due to diabetic nephropathy. Since the patient also had hyperkalaemia, he started haemodialysis on the day of admission. The patient also received hemoperfusion therapy because of possible amantadine intoxication. Blood amantadine concentration was 2800 ng/mL. The drug was discontinued. 1 day after discontinuation: The patient received hemoperfusion therapy (2 hours) and hemofiltration dialysis. Hemofiltration dialysis was performed three times a week thereafter. Blood amantadine concentration was 3500 ng/mL. 3 days after discontinuation: The movements involuntary were resolved. The orientation was improved. Blood amantadine concentration was 2200 ng/mL. 8 days after discontinuation: Blood amantadine concentration was 1200 ng/mL. 11 days after discontinuation: The patient opened his eyes to calling, but was unable to speak. Head CT revealed suggested multiple penetrating artery infarctions. 27 days after discontinuation: Since the blood amantadine concentration was 64 ng/mL, the patient switched to haemodialysis. 40 days after discontinuation: Because of disuse muscle atrophy after hospitalization, the patient had delayed gait recovery, but eventually became able to walk after rehabilitation.	
	Concomitant medications: candesartan cilexetil, nifedipine, calcium polystyrene sulfonate, oxybutynin hydrochloride, aspirin/dialuminate, magnesium oxide, insulin human (Genetical recombination)				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Multiple cerebral infarction [short-stepped gait] (hypertension, chronic renal failure, uraemic encephalopathy)	150 mg 18 days	**Cognitive disorder, movement disorder, and generalised convulsion** Approx. 17 years before administration: The patient started haemodialysis due to chronic renal failure. Approx. 5 years before administration: Cerebral infarction (left thalamus to posterior limb of internal capsule) developed. 38 days before administration: The patient was hospitalized because of pyrexia (pneumonia). On day 1 of administration: Amantadin hydrochloride at 150 mg was started for the treatment of right hemiparesis and short-stepped limping. On day 8 of administration: At midnight, the patient fell on the floor when he got out of his bed with a basin, stating "I was going to take a bath". In the evening, he almost fell on his back while eating. Increased unsteady gait was observed. He was also lisping. On day 9 of administration: The patient sat down by his bedside and could not move while trying to go to the bathroom. He had slurred speech. On day 13 of administration: The patient was fed by a helper because he could not use his hands well. He choked on liquids. On day 14 of administration: Truncal ataxia and disorientation to time were observed. Uraemic encephalopathy was considered. Intramuscular dexamethasone sodium phosphate was started. The patient was unable to hold arms extended. On day 15 of administration: Head MRI revealed punctate infarction lesions in the deep white matter near the frontal horn of lateral ventricle. The patient was able to hold arms extended. On day 16 of administration: Hallucination, dyslalia, and unrest (abnormal behaviour) were observed. On day 17 of administration: One-minute generalised tonic convulsion, hallucination, and abnormal behaviours such as trying to catch something in the air were observed. On day 18 of administration (day of discontinuation): Generalised convulsion, dyslalia, and dysphagia were observed. Approximately 1 hour later, the patient had jitteriness and unrest. It was considered to be a result of increased blood amantadine concentration. Thus, amantadine hydrochloride was discontinued. Blood amantadine concentration was 2300 ng/mL. The hallucination and the associated abnormal behaviours were persisted. Jitteriness was noted.	Company report

				1 day after discontinuation: The symptoms began to improve, but jitteriness, soliloquy, and dyslalia were prominent. 3 days after discontinuation: The patient was able to hold arms extended and also to make conversations. 5 days after discontinuation: Haemodialysis filtration (HDF) was performed. The patient became able to eat by himself. 6 days after discontinuation: The patient had infrequent jitteriness and could make conversations. 7 days after discontinuation: HDF was performed again. 9 days after discontinuation: The symptoms were almost resolved. Dexamethasone sodium phosphate was discontinued.	
	Concomitant medications: precipitated calcium carbonate, ticlopidine hydrochloride, estazolam, sennoside, amezinium metilsulfate				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 60s	Hypobulia [cerebral haemorrhage] (hypertension, diabetes mellitus, hyperuricaemia, chronic renal failure, diabetic retinopathy)	150 mg 70 days	**Myoclonus, delirium, and exacerbation of chronic renal failure** Approx. 18 years before administration: Hypertension was diagnosed. Approx. 11 years before administration: Diabetes mellitus was diagnosed. Approx. 2 years and 8 months before administration: The patient received outpatient treatment for hypertension and diabetes mellitus. Approx. 1 year before administration: The patient was hospitalized for control of hypertension and diabetes mellitus (for 22 days). Approx. 5 months before administration: The patient had malignant hypertension and was hospitalized for blood pressure control (for 25 days). 11 days before administration: Disturbances of consciousness, conjugate deviation of left eye, and right hemiplegia developed. Left thalamus haemorrhage was diagnosed by CT. 10 days before administration: The patient also developed haemorrhage into ventricle-associated acute hydrocephalus and received external ventricular drainage. On day 1 of administration: Amantadine hydrochloride at 150 mg was started. The hypobulia was gradually improved and the patient's rehabilitation went well. On day 56 of administration: The patient was transferred to a rehabilitation hospital. She had eating disorder and poor water intake resulting from environmental change. On day 69 of administration: Delirium and systemic myoclonus developed. On day 70 of administration (day of discontinuation): Amantadine hydrochloride was discontinued. 2 days after discontinuation: The patient was rehospitalized in our hospital with no improvement in delirium and myoclonus. Fluid replacement and medication adjustment were performed. Blood amantadine concentration was 2800 ng/mL. 3 days after discontinuation: Spinal amantadine concentration was 2200 ng/mL. 5 days after discontinuation: The symptoms (delirium and myoclonus) were gradually improved. 8 days after discontinuation: The symptoms were resolved. The systemic conditions were stable.	Company report
	Concomitant medications: nifedipine, temocapril hydrochloride, candesartan cilexetil, carvedilol, doxazosin mesilate, methyldopa, lafutidine, allopurinol, nicergoline				

2 Ceftriaxone Sodium

Brand Name (name of company)	Sefirom Intravenous 0.5 g and 1 g (Maruko Pharmaceutical Co., Ltd.) Cefxone Intravenous 1 g (Shiono Chemical Co., Ltd.) Ceftriaxone Sodium Intravenous 1 g "TX" (TRY-X Co., Ltd.) Ceftriaxone Sodium for Intravenous 1 g bag "NP" (Nipro Pharma Corporation) Ceroneed Intravenous 1 g (Sawai Pharmaceutical Co., Ltd.) Liasophin for Intravenous Injection 0.5 g and 1 g (Chemix Inc.) Rozeclart Intravenous 1 g, Rozeclart Kit for Intravenous Infusion 1 g (Taiyo Yakuhin Co., Ltd.) Rocephin Intravenous 0.5 g and 1 g, Rocephin Infusion Bag 1 g (Chugai Pharmaceutical Co., Ltd.) Rocemerck Intravenous 1 g (Merck Pharma Ltd.)
Therapeutic Category	Antibiotics acting mainly on gram-positive and gram-negative bacteria
Indications	○ Susceptible strains Ceftriaxone-susceptible *Staphylococcus sp., Streptococcus sp., Pneumococcus sp., Gonococcus, Escherichia coli, Citrobacter sp., Klebsiella sp., Enterobacter sp., Serratia sp., Proteus sp., Morganella morganii, Providencia sp., Haemophilus influenzae, Peptostreptococcus sp., Bacteroides sp., Prevotella sp.* (excluding *Prevotella bivia*) ○ Indications Sepsis, laryngopharyngitis, tonsillitis, acute bronchitis, pneumonia, lung abscess, empyema thoracis, secondary infection in chronic respiratory lesions, cystitis, pyelonephritis, epididymitis, urethritis, cervicitis, pelvic inflammatory disease, proctitis, peritonitis, intra-abdominal abscess, cholecystitis, cholangitis, bartholinitis, intrauterine infection, uterine adnexitis, parametritis, purulent meningitis, keratitis (including corneal ulcer), otitis media, sinusitis, jaw cellulitis, jaw inflammation

<<**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 with an increase in AST (GOT), ALT (GPT), γ-GTP etc, jaundice may occur. Patients should be carefully monitored through periodic testing etc. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to June 30, 2006) (events for which a causality to the drug could not be denied) • Hepatitis fulminant etc.: 3 cases (of which 3 had fatal cases) The number of patients treated with Ceftriaxone for a year estimated by MAH: approximately 1.04 million (July 2005 to June 2006) Marketed in Japan in: 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Infectious disease prophylaxis, suspected pneumonia (cardiac failure, atrioventricular block complete)	1 g 7 days	**Hepatitis fulminant** 12 days before administration: Metildigoxin treatment was completed. 9 days before administration The patient was hospitalized with senile dementia. She became wheelchair-dependent. HBs antigen (–), HCV-3rd (–) 8 days before administration: Ultrasound examination results: no abnormal findings in the biliary system. 6 days before administration: Atrioventricular block complete developed. On day 1 of administration: Dyspnoea (cardiac failure) developed. A central venous catheter was placed. Oxygen inhalation therapy was initiated. Morphine hydrochloride and nitroglycerin were started for the treatment of cardiac failure. Concomitant pneumonia was suspected by chest X-ray. In addition, the CRP was (2+). Ceftriaxone sodium was started. Severity of cardiac failure at onset (NYHA classification) was Grade IV. Concomitant chest pain, seizure, and cardiac failure congestive were noted. The result of methyldigoxin concentration measurement (specimen: blood) was 1.0 ng/mL (normal range). On day 4 of administration: EF value was 25%. The cardiac failure was temporarily improved. On day 6 of administration: The patient developed general malaise, skin coloring yellow, disturbances of consciousness, and somnolence. On day 7 of administration (day of discontinuation): Marked increase in transaminase values and Grade 3 coma hepatic were noted. Ceftriaxone sodium was discontinued. 1 day after discontinuation: Fresh frozen human plasma (FFP), gabexate mesilate, liver extract/flavin adenine dinucleotide, and glycyrrhizin/glycine/cysteine were administered. 2 days after discontinuation: FFP, gabexate mesilate, liver extract/flavin adenine dinucleotide, and glycyrrhizin/glycine/cysteine were administered. 3 days after discontinuation: FFP, gabexate mesilate, liver extract/flavin adenine dinucleotide, and glycyrrhizin/glycine/cysteine were administered.	Company report

				4 days after discontinuation: The patient died of multi-organ failure (heart/kidneys/liver). Autopsy: not performed.	
	Concomitant medications: ranitidine hydrochloride, morphine hydrochloride, nitroglycerin, furosemide, citicoline, multivitamin product for hyperalimentation				

Clinical Laboratory Values

	9 days before administration	On day 1 of administration	On day 4 of administration	On day 7 of administration (day o f discontinuation)	2 days after discontinuation
AST (GOT) (IU/L)	36	155	89	2257	1310
ALT (GPT) (IU/L)	25	128	102	1468	1424
Total bilirubin (mg/dL)	0.9	2.4	1.1	2.4	3.8
Platelet count ($\times 10^4/mm^3$)	13.1	11.2	10.8	10.1	6
WBC ($/mm^3$)	5100	7700	9700	12400	9800
CRP	(2+)	(3+)	(3+)	(4+)	(3+)

AST: Asparate Aminotransferase ALT: Alanine Aminotransferase
WBC: White Blood Cell 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 80s	Bronchitis (asthma, diabetes mellitus)	2 g 2 days	**Hepatitis fulminant** Approx. 13 days before administration: The patient developed bronchitis-induced asthma bronchial. Severity: severe (difficulty moving due to dyspnoea), SpO_2 91%, O_2 at 3 L by mask 8 days before administration: Asthma developed. The patient was treated with theophylline, procaterol hydrochloride, carbocisteine, and norfloxacin (until on day 1 of administration). On day 1 of administration: The patient visited the hospital with grand mal of asthma bronchial. He was hospitalized. A nebulizer treatment didn't work. Methylprednisolone sodium succinate and aminophylline were administered. Bronchitis symptoms were noted. CRP was 2 mg/dL. Ceftriaxone sodium was started. Pathogenic bacteria test (ear) results: pseudomonas aeruginosa On day 2 of administration (day of discontinuation): Ceftriaxone sodium, methylprednisolone sodium succinate, and aminophylline were administered (in the morning). AST (GOT) 583 IU/L, ALT (GPT) 325 IU/L. Drug-induced liver disorder was suspected. Ceftriaxone sodium, methylprednisolone sodium succinate, and aminophylline were discontinued in the afternoon. 2 days after discontinuation: Japan Coma Scale (JCS) increased to 3 digits. AST (GOT) 4660 IU/L, ALT (GPT) 2930 IU/L, PT 11%. Hepatitis fulminant was suspected because of Grade III coma hepatic. Plasmapheresis (FFP 30 units). Method: simple plasmapheresis	Company report

				3 days after discontinuation: Plasmapheresis: PT 28% 4 days after discontinuation: Plasmapheresis: PT 34% 5 days after discontinuation: PT 33%, JCS decreased to 2 digits. 7 days after discontinuation: PT 19%, Plasmapheresis was conducted. 8 days after discontinuation: SpO_2 was ≥95%, but suddenly dropped to between 70% and 80%. SpO_2 did not improve with 10 L of O_2 by mask. The patient was intubated. Bradycardia occurred, followed by cardiac arrest. Resuscitation was attempted, but the patient died. Cause of death: hepatitis fulminant [Evaluation items related to hepatic function disorder] • Initial symptoms: pyrexia and coma • Hepatitis panel: IgM-HA antibody, HBs antigen, HBs antibody, HBc antibody: (−) • Autoantibody: (−) • Drug susceptibility test: DLST (performed 2 days after discontinuation) Methylprednisolone sodium succinate: (−) • Alcohol intake: none • Liver biopsy: not performed • Ultrasound examination (performed 2 days after discontinuation): no abnormal findings	
	Concomitant medications: methylprednisolone sodium succinate, aminophylline, theophylline, procaterol hydrochloride, carbocisteine, norfloxacin, insulin human (Genetical recombination), prednisolone, fluticasone propionate				

Clinical Laboratory Values

	On day 1 of administration	On day 2 of administration (day of discontinuation)	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation	7 days after discontinuation	8 days after discontinuation
AST (GOT) (IU/L)	33	583	4660	1165	276	135	63	51
ALT (GPT) (IU/L)	16	325	2930	1011	385	197	142	55
Total bilirubin (mg/dL)	0.8	1.5	2.1	2.3	3.7	4.7	7.7	6.4
Direct bilirubin (mg/dL)	--	0.8	--	--	--	--	--	--
Albumin (g/dL)	4.2	--	--	3.4	3.5	3.6	3.2	2.8
Platelet count ($\times 10^4/mm^3$)	20.9	16.1	5.9	4.0	3.8	5.1	4.1	2.6
WBC ($/mm^3$)	7500	9600	11600	9900	11900	14200	15500	30700
PT (sec)	--	--	32.1	18.5	16.5	16.9	23.2	19.1
PT (%)	--	--	11	28	34	33	19	27
CRP (mg/dL)	2.25	2.31	2.53	--	--	0.43	1.33	3.22

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
WBC: White Blood Cell
PT (sec): Prothrombin Time (sec)
PT (%): Prothrombin Activity (%)
CRP: C-Reactive Protein

3

Revision of PRECAUTIONS

(No. 181)

This section presents details of revisions of PRECAUTIONS in package inserts and brand names of drugs that have been revised according to the Notification after the issue before previous one (Pharmaceuticals and Medical Devices Safety Information No. 228) (excluding those presented in "2. Important Safety Information" of this Bulletin), together with reference materials.

<Antipyretics and analgesics, anti-inflammatory agents>

1 Sulindac

[Brand Name]	Clinoril Tablets 50 and 100 (Banyu Pharmaceutical Co., Ltd.) and others
[Adverse Reactions (clinically significant adverse reactions)]	**Acute renal failure, acute nephritis interstitial, nephrotic syndrome:** Oliguria, haematuria, proteinuria, BUN/blood creatinine increased, hyperkalaemia, hypoalbuminaemia, etc. may occur.
<Reference Information>	Company report

<Antiarrhythmic agents>

2 Pilsicainide Hydrochloride (oral dosage form)

[Brand Name]	Sunrythm Capsules 25 mg and 50 mg (DAIICHI ASUBIO PHARMA CO., LTD.) and others
[Adverse Reactions (clinically significant adverse reactions)]	**Ventricular fibrillation, ventricular tachycardia, sinus arrest, atrioventricular block complete, syncope:** These adverse reactions may occur. Electrocardiography should be frequently performed. If abnormal findings are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

<Antiarrhythmic agents>

3 Pilsicainide Hydrochloride (injectable dosage form)

[Brand Name]	Sunrythm Injection 50 (DAIICHI ASUBIO PHARMA CO., LTD.)
[Adverse Reactions (clinically significant adverse reactions)]	**Ventricular fibrillation, ventricular tachycardia, sinus arrest, atrioventricular block complete, syncope:** These adverse reactions may occur. Continuous monitoring of electrocardiography should be performed. If abnormal findings are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

4 Bepridil Hydrochloride

[Brand Name] Bepricor Tablets 50 and 100 (Nippon Organon K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Interstitial pneumonia:** Interstitial pneumonia may occur. If pyrexia, cough, dyspnoea, abnormal chest sound (crepitations) etc. is observed, administration should be immediately discontinued and appropriate measures such as administration of adrenocortical hormones should be taken in addition to prompt examinations such as chest X-ray.

<Reference Information> Company report

5 Carvedilol

[Brand Name] Artist Tablets 1.25 mg, 2.5 mg, 10 mg, and 20 mg (Daiichi Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Acute renal failure :** Acute renal failure may occur. Patients should be carefully monitored. If abnormalities are observed, appropriate measures such as discontinuation of treatment should be taken.

<Reference Information> Company report

6 Trimebutine Maleate

[Brand Name] Cerekinon Fine Granules, Cerekinon Tablets (Tanabe Seiyaku Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice:** Hepatic function disorder with an increase in AST (GOT), ALT (GPT), Al-P, LDH, γ-GTP etc, jaundice 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

7 Aluminum Potassium Sulfate/Tannic Acid

[Brand Name] Zione Injection, Zione Injection/Lidocaine (Mitsubishi Pharma Corporation)

[Important Precautions] Serious rectal ulcer and rectal stenosis etc. may occur following administration of this drug. Patients should be followed-up periodically after treatment. Prior to administration, patients should be adequately advised on treatment, including adverse reactions associated with this product. Patients should also be instructed to consult a primary doctor immediately, if abnormalities such as haemorrhage and anal pain are noted.

[Adverse Reactions (clinically significant adverse reactions)] **Rectal ulcer:** Rectal ulcer associated with haemorrhage and anal pain etc. may occur following administration of this drug. Patients should be periodically monitored after treatment. If such symptoms are observed, appropriate measures such as administration of antibiotics/suppositories should be taken.
Rectal stenosis: Rectal stenosis may occur following administration of this drug. Patients should be periodically monitored after treatment. If such symptoms are observed, appropriate measures such as incision of stenosis and bougienage should be taken.

<Reference Information> Company report

8 <Synthetic antibacterials> Moxifloxacin Hydrochloride

[Brand Name] Avelox Tablets 400 mg (Bayer Yakuhin, Ltd.)

[Important Precautions] Syncope, loss of consciousness, and dizziness may occur. Patients should be advised to refrain from engaging in potentially hazardous operations of machinery including driving a car. Prior to treatment, patients should be fully informed of these potential adverse reactions.

[Adverse Reactions (clinically significant adverse reactions)] **Syncope and loss of consciousness:** Syncope, loss of consciousness, depressed level of consciousness may occur. Appropriate measures such as discontinuation of treatment should be taken in such cases.

<Reference Information> Company report

9 <Vaccines> Freeze-dried Live Attenuated Varicella Vaccine

[Brand Name] Freeze-dried Live Attenuated Varicella Vaccine "BIKEN" (Research Institute for Microbial Diseases, Osaka University)

[Precautions of Dosage and Administration] Target population

This vaccine is used for persons aged 12 months and older without history of varicella and to whom the following (1) to (6) apply.

However, persons to whom the following (1) to (6) apply should not receive the vaccination when they are expected to have peripheral lymphocyte count decreased or immunological competence decreased by treatment or any reasons within 2 weeks after vaccination. [Those persons may become susceptible to infection with the vaccine virus, such as developing disseminated symptoms.]

<Reference Information> Company report

10 Over the counter drugs Containing Ibuprofen

[Brand Name] Eve (SSP Co., Ltd.), Feria (Takeda Pharmaceutical Company Limited), Ringl IB Gel Capsules (Sato Pharmaceutical Co., Ltd.) and others

[When not to use the product] These products should not be used in the following persons.

Children aged under 15

<Reference Information> Company report

11 Over the counter drugs Containing Scopolamine Butylbromide

[Brand Name] Buscopan-A Tablets, Buscopan-M Capsules (SSP Co., Ltd.) and others

[When not to use the product] These products should not be used in the following persons.

Persons with a history of allergic reactions to this product

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

Shock (anaphylaxis): Immediately after administration, urticaria, oedema, chest distress, etc. may occur concurrently with pallor facial, cold hands and feet, cold sweat, and respiratory discomfort.

<Reference Information> Company report

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12 Over the counter drugs
Products Containing Trimebutine Maleate

[Brand Name] Inoseaact (Sato Pharmaceutical Co., Ltd.), Tanabe Gastrointestinal drug <Tuning>, Tanabe Gastrointestinal Granules (Tanabe Seiyaku Co., Ltd.), Pansiron Trim <Granules>, Pansiron Trim <Tablets> (ROHTO Pharmaceutical Co., Ltd.) and others

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

Hepatic function disorder: General malaise, jaundice (skin and white of the eyes become yellow) may occur.

<Reference Information> Company report

4

List of products subject to Early Post-marketing Phase Vigilance

(As of November 1, 2006)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Clopidogrel Sulfate / Plavix Tablets 25 mg and 75 mg	Sanofi-Aventis K.K.	May 8, 2006
Silodosin / Urief Cap. 2 mg and 4 mg	Kissei Pharmaceutical Co., Ltd.	May 11, 2006
Tosufloxacin Tosilate / Ozex Ophthalmic Solution 0.3%	Toyama Chemical Co., Ltd.	May 11, 2006
Follitropin Alfa (Genetical recombination) / Gonalef for S.C. Injection 75 and 150	Serono Japan Co., Ltd.	May 11, 2006
Letrozole / Femara Tablets 2.5 mg	Novartis Pharma K.K.	May 11, 2006
Loxoprofen Sodium / Loxonin PAP 100 mg	LEAD CHEMICAL Co., Ltd.	May 23, 2006
Aripiprazole / Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%	Otsuka Pharmaceutical Co., Ltd.	June 8, 2006
Solifenacin Succinate / Vesicare Tablets 2.5 mg and 5 mg	Astellas Pharma Inc.	June 8, 2006
Tolterodine Tartrate / Detrusitol Capsules 2 mg and 4 mg	Pfizer Japan Inc.	June 8, 2006
Amphotericin B / AmBisome for Intravenous Infusion 50 mg	Dainippon Sumitomo Pharma Co., Ltd.	June 20, 2006
Magnesium Sulfate/Glucose / Magsent Injection 100 mL	TOA Pharmaceuticals Co., Ltd.	June 20, 2006
Sertraline Hydrochloride / Jzoloft Tablets 25 mg and 50 mg	Pfizer Japan Inc.	July 7, 2006
Somatropin (Genetical recombination) / Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg[*1]	Pfizer Japan Inc.	July 26, 2006
Inulin / Inulead Inj.	FUJIYAKUHIN Co., Ltd.	August 22, 2006
Alendronate Sodium Hydrate / Fosamac Tablets 35 mg	Banyu Pharmaceutical Co., Ltd.	September 15, 2006
Alendronate Sodium Hydrate / Bonalon Tablet 35 mg	Teijin Pharma Limited	September 15, 2006
Itraconazole / Itrizole Oral Solution 1%	Janssen Pharmaceutical K.K.	September 15, 2006

Temozolomide Temodal Capsules 20 mg and 100 mg	Schering-Plough K.K.	September 15, 2006
Budesonide Pulmicort Respules 0.25 mg and 0.5 mg	AstraZeneca K.K.	September 15, 2006
Entecavir Hydrate Baraclude Tablets 0.5 mg	Bristol Pharmaceuticals Y.K.	September 21, 2006
Cetrorelix Acetate Cetrotide for Injection 0.25 mg and 3 mg	Nippon Kayaku Co., Ltd.	September 21, 2006
Manganese Chloride Tetrahydrate Bothdel Oral Solution 10	Meiji Dairies Corporation	September 25, 2006
Gabapentin Gabapen Tablets 200 mg, 300 mg, and 400 mg	Pfizer Japan Inc.	September 25, 2006
Busulfan	Kirin Brewery Company, Limited	October 10, 2006[*2]
Busulfex Injection 60 mg		October 20, 2006[*3]
Fexofenadine Hydrochloride Allegra Tablets 60 mg[*4]	Sanofi-Aventis K.K.	October 20, 2006

*1: An additional indication for "adult growth hormone hyposecretion (for severe cases only)"
*2: For the adult dose initially approved
*3: An additional administration for "pediatrics"
*4: An additional administration for "pediatrics (aged 7 and older)"