Pharmaceuticals and Medical Devices Safety Information

No. 213 May 2005

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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 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).

Pharmaceuticals and Medical Devices Safety Information

No. 213 May 2005

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

1

Impact of X-ray CT apparatus on implantable cardiac pacemaker (Medtronic InSync 8040)

(1) Outline

The Medtronic InSync 8040 is an implantable cardiac pacemaker approved with the indication and usage for "reduction of symptoms of severe cardiac failure in those patients who remain symptomatic despite sufficient medical therapy, and have a left ventricular ejection fraction ≤35% and a QRS duration ≥130 ms" in May 2003.

Over a 1 year period from the initial marketing in April 2004 until the end of March 2005, there were 11 reports of adverse event in patients implanted with this product which involved the partial electrical resetting (hereafter, "reset") of this product during X-ray CT scan.

It was discovered through investigation that, in all cases, this event occurred when X-rays from X-ray CT apparatus used in clinical practice were irradiated onto this product, and that oversensing of the pacemakers occurred while the X-rays were being irradiated or passing over the pacemakers.

As a structural defect within the product could not be denied, and as this could be a serious health hazard in the cases that countermeasures are not taken immediately after resetting occurs, it was decided that immediate measures should be taken.

(2) Instructions issued to manufacturers

① It was decided that revisions including the following additions should be made to the package insert of Medtronic InSync 8040 and that healthcare providers such as physicians and radiological technicians in medical institutions using this product should be cautioned.

a) The following statement should be indicated in the "Contraindications" section: "[Relative contraindications] The implanted region of this product should not be irradiated with X-rays from an X-ray CT apparatus. (Doing so may cause the pacemaker to reset.) If X-ray irradiation cannot be avoided, it should be conducted at the institution where this product was implanted or at a follow-up institution while monitoring the patient's pulse under supervision of the specialists capable of promptly canceling the reset by its programmer if it should occur [refer to "Interactions"]."

b) Similarly, the X-ray CT apparatus should be mentioned under the "Important Precautions" and "Interactions" sections in PRECAUTIONS, and the content of "Interactions" (clinical symptoms, treatment methods, mechanisms, and risk factors, etc.) should be briefly described.

② Appropriate countermeasures such as mention in the patient handbook should be taken to ensure that patients implanted with this product do not carelessly receive an X-ray examination at another institution.

③ It was decided that the cause of resetting from X-ray irradiation should be investigated, structural changes etc. to the device should be considered, and safety measures should be promptly implemented. However, if it is acknowledged that such changes will necessitate making partial changes to the approved items, application for the approval of partial changes should be swiftly conducted.

MHLW is presently instructing related companies to verify the effect on other similar devices.

(3) Request for medical institutions

① The implanted region of this product should not be irradiated with X-rays from an X-ray CT apparatus.

② When X-ray irradiation on the site implanted with this device is inevitably conducted for treatment, X-ray irradiation should be performed while monitoring the patient's pulse under supervision of the specialists capable of promptly canceling the reset by its programmer if it should occur.

③ Also, provide sufficient explanation to the patient to ensure that patient already implanted with this device does not carelessly receive an X-ray examination at another institution.

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 previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 211).

1 Candesartan Cilexetil, Telmisartan, Valsartan, Losartan Potassium

Brand Name (name of company)	**Candesartan Cilexetil** Blopress Tablets 2, 4, 8, and 12 (Takeda Pharmaceutical Company Limited) **Telmisartan** Micardis Capsules 20 mg and 40 mg, Micardis Tablets 20 mg and 40 mg (Nippon Boehringer Ingelheim Co., Ltd.) **Valsartan** Diovan Tablets 20 mg, 40 mg, 80 mg, and 160 mg (Novartis Pharma K.K.) **Losartan Potassium** Nu-lotan Tablets 25 and 50 (Banyu Pharmaceutical Co., Ltd.)
Therapeutic Category	Antihypertensives
Indications	**Candesartan Cilexetil** Hypertension, renal parenchymal hypertension **Telmisartan, Valsartan, Losartan Potassium** Hypertension

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

[Adverse Reactions (clinically significant adverse reactions)]	**Hypoglycemia:** Since hypoglycemia may occur (liable to occur in patients on diabetic therapy), close observation should be made. If feeling of weakness or hungry, cold sweat, tremor of hands, decreased mental concentration, convulsions, disturbed consciousness, etc. 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 80s	Hypertension (mild diabetes mellitus, mild function kidney decreased, multiple cerebral infarction, anaemia, gastritis erosive)	8 mg 162 days	**Hypoglycaemia** Height 146 cm, weight 33 kg 1 month before administration: The patient was hospitalized for gastritis erosive. On day 1 of administration: Administration of candesartan cilexetil was started to treat hypertension. On day 160 of administration: Diet consisted of portions for 1 normal adult taken 3 times/day. Dinner time was 19:00. Exercise was limited to daily activities (walking to the toilet and washroom; did not go outdoors). On day 161 of administration: The patient did not get out of bed in the morning, was staring blankly out into space (consciousness disturbed), and paralysis of the left hand and foot was confirmed. Upon immediate examination at another hospital, hypoglycaemia (28 mg/dL) was confirmed. Later, convulsive seizure in both upper limbs manifested. 5% glucose infusion was conducted. Blood glucose levels only rose to 40 to 60 mg/dL despite intravenous administration of 50% glucose. On day 162 of administration: The patient was examined at this hospital for complete medical examination and treatment of hypoglycaemia. On day 163 of administration (day of discontinuation): Upon implementation of 10% glucose infusion and discontinuation of candesartan cilexetil administration, blood glucose levels gradually improved. Consciousness disturbed also improved. 2 days after discontinuation: Pituitary gland CT: there were no abnormalities. ACTH 85 pg/mL, cortisol 20.1 μg/dL. TSH, FT_3, and FT_4 were within the normal range. 3 days after discontinuation: The patient recovered from hypoglycaemia. Abdominopelvic CT: there were no abnormalities to liver, gallbladder, or pancreas. 5 days after discontinuation: Chest CT: there were no abnormalities other than old pleurisy. 6 days after discontinuation: Blood glucose was 126 mg/dL during 10% glucose drip infusion, which was discontinued before lunch. Blood glucose 3 hours after eating lunch was 64 mg/dL. At this time, IRI and CPR levels were high at 18.1 μU/mL and 5.5 ng/mL, respectively. Hyperglycemic hormones (ACTH, glucagon, noradrenaline, adrenaline, dopamine and cortisol) were being excreted normally. 11 days after discontinuation: 75 g glucose tolerance test was conducted. 12 days after discontinuation: Hypoglycaemia was not observed even after discontinuation of glucose infusion.	Company report

				13 days after discontinuation: Starvation test was negative for insulin secreting tumors (after 24 hour fast, blood glucose was 78 mg/dL; IRI was 4.0 μU/mL; CPR was 0.8 ng/mL). 34 days after discontinuation: Gallium tumor scintigram: there was no abnormal accumulation and malignancy was negative. Later, hypoglycemia was not observed after eating regularly and administration of voglibose.	
	Concomitant medications: rebamipide, cimetidine, aluminum hydroxide gel/magnesium hydroxide				

75 g glucose tolerance test

	0 minute	30 minutes	60 minutes	120 minutes	180 minutes	240 minutes	300 minutes
Blood glucose levels (mg/dL)	100	195	220	209	162	153	76
IRI (μU/mL)	9.7	40.7	74.4	134.5	104.8	59.8	17.3

IRI: Immunoreactive Insulin

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.) Ceroneed Intravenous 1 g (Sawai Pharmaceutical Co., Ltd.) Liasophin for Intravenous Injection 0.5 g and 1 g (Chemix Inc.) Rozeclart Intravenous 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 Hoei Ltd.)
Therapeutic Category	Acting mainly on gram-positive and gram-negative bacteria
Indications	○Susceptible strains Ceftriaxone susceptible strains of *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, pyothorax, secondary infection of chronic respiratory lesions, cystitis, pyelonephritis, epididymitis (epididymal inflammation), urethritis, cervicitis, pelvic inflammatory disease, proctitis, peritonitis, intraperitoneal abscess, cholecystitis, cholangitis, bartholinitis, intrauterine infection, uterine adnexitis, parametritis, purulent meningitis, keratitis (including corneal ulcer), otitis media, sinusitis, cellulites around jaw bone, jaw inflammation

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

[Adverse Reactions (clinically significant adverse reactions)]

Gallstones, intrabiliary debris: Gallstones composed of ceftriaxone and intrabiliary debris during or after administration of this drug may cause cholecystitis, cholangitis, and pancreatitis etc. If symptoms of abdominal pain etc. occur, discontinue administration, immediately conduct abdominal ultrasound tests etc., and take appropriate measures. Moreover, many of these cases have occurred from the high dosing in children with serious infectious disease.

Calculus renal and calculus urinary: It has been reported overseas that calculus renal and calculus urinary composed of ceftriaxone developed during or after the administration of this drug leading to symptoms of urine output decreased, urination impaired, haematuria, and crystalluria etc., as well as acute postrenal failure. If these symptoms are observed, discontinue administration and immediately take appropriate measures.

<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	Male under age of 10	Upper respiratory inflammation, sinusitis (calcifying epithelioma of the left anterior ear)	1.4 g 12 days	**Cholelithiasis** 8 days before administration: Proteinuria developed (cause unknown). 1 day before administration: The patient was hospitalized. Intradermal test with this drug was conducted (results: negative). On day 1 of administration: Administration of this drug was started to treat upper respiratory inflammation and sinusitis (mild). On day 12 of administration (day of discontinuation): Administration of this drug was discontinued and oral administration of clarithromycin, carbocisteine, and mequitazine was started. 3 days after discontinuation: As proteinuria persisted, oral administration of dipyridamole was started. 7 days after discontinuation: Intense epigastric pain developed. Hydroxyzine pamoate and glycerin enema was implemented. 8 days after discontinuation: No abnormalities were found in abdominal X-ray and stool culture. Dipyridamole was discontinued due to recurrence of epigastric pain in the afternoon. 9 days after discontinuation: Abnormality was discovered through abdominal echogram. Hepatic function abnormal developed. 11 days after discontinuation: Fat-restricted diet and administration of ursodeoxycholic acid were started. I.V. drip infusion of liver extract preparation was conducted. 13 days after discontinuation: Gallbladder stones were found through abdominal CT. [Findings] Small, narrow calcification was found in the gallbladder. It was considered multiple calcifications. There was mild hypertrophy of the gallbladder wall. No dilation of the intrahepatic bile duct and common bile duct was observed. Formation of calcified stone at the head of the pancreas was difficult to discern. There was no clear enlargement of abdominal lymph nodes. There was no ascites. [Diagnosis] small gallbladder stones with chronic cholecystitis. Biochemical data suggested that small common bile duct stones may have already passed. 16 days after discontinuation: Epigastric pain developed. Abdominal echogram was performed. As false stones were shrinking, only a follow-up was conducted. 23 days after discontinuation: There were no symptoms and echogram showed disappearance of false stones. 25 days after discontinuation: The patient was discharged from the hospital.	Company report
	Concomitant medications: none				

Clinical Laboratory Values

	1 day before administration	On day 4 of administration	9 days after discontinuation	11 days after discontinuation	13 days after discontinuation	16 days after discontinuation	19 days after discontinuation
Total bilirubin (mg/dL)	--	--	0.9	0.5	0.5	0.4	0.5
Direct bilirubin (mg/dL)	--	--	0.4	0.2	0.2	0.2	0.2
AST (GOT) (IU/L)	23	29	624	40	33	23	26
ALT (GPT) (IU/L)	15	16	845	285	155	56	47
Al-P (IU/L)	654	531	912	700	707	635	712
LDH (IU/L)	520	632	804	446	296	256	269
γ-GTP (IU/L)	--	--	135	104	130	94	107
CRP (mg/dL)	0.0	0.0	0.1	0.1	0.0	0.0	0.0
Protein urine (mg/dL)	496	55	89	10	32	38	24

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	Female under age of 10	Meningitis bacterial (none)	1.9 g 17 days	**Bile duct stones** 2 days before administration: Pyrexia and vomiting developed. 1 day before administration: As nuchal rigidity was confirmed, the patient was hospitalized for suspected meningitis. Spinal fluid and blood culture at time of hospitalization: *H. influenzae* positive. On day 1 of administration: After hospitalization, until the pathogenic bacteria were ascertained, the treatment was started with administration of this drug at 1.9 g (twice a day) and panipenem/betamipron at 2.4 g (4 times a day) for meningitis bacterial. Dexamethasone was administered concurrently. On day 3 of administration: After identifying the bacteria, single administration of this drug was conducted (for a total of 17 days). On day 14 of administration: After eating breakfast, the patient experienced abdominal pain. The symptom improved over the course of observation. On day 17 of administration (last day of administration): Before daybreak, the patient experienced abdominal pain while sleeping. The symptom improved over the course of observation. 3 days after completion: There were no neurologic sequelae. Meningitis improved, and the patient was discharged. During hospitalization, there were no abnormalities with hepatobiliary enzymes. Unknown: The patient complained of abdominal pain on several occasions after she was discharged. But the symptoms were naturally improved.	Company report

				10 days after completion: While sleeping during the evening, the patient woke up due to abdominal pain. About 1 hour later, the symptom improved through enema. 16 days after completion: The patient experienced abdominal pain after dinner. She vomited once during the night. The symptoms improved through rectal administration of domperidone. 25 days after completion: The patient had abdominal pain since morning. Although it was improved during the daytime, the symptom became aggravated from night. 26 days after completion: As increase in hepatobiliary enzymes was confirmed by blood test, the patient was rehospitalized. During hospitalization, hypochondrium pain right was observed. Apart from increased hepatobiliary enzymes, no abnormalities were confirmed by blood and urinary tests. Gallbladder and bile duct stones were visualized from an abdominal echogram and CT scan. Multiple gallbladder and bile duct stones as big as 3 to 4 mm and gallbladder wall thickening were confirmed. The symptoms immediately improved through rest, abstinence from food or drink (diet therapy), and fluid replacement (infusion), and test findings were normalized. Abdominal echogram found that several 3 to 4 mm sized gallbladder stones had not been resolved. 33 days after completion: In the afternoon, there was mild abdominal pain. 38 days after completion: Abdominal pain increased in the afternoon. Immediately after, the patient vomited once, then improved. 39 days after completion: There was no abdominal pain. No bile duct stones were confirmed through abdominal echogram. As the result of blood test, no increase in hepatobiliary enzymes was confirmed. 41 days after completion: The patient had abdominal pain immediately after she ate cream bun after breakfast. Tenderness extended from right hypochondrium to umbilical region. The pain got better after about 10 minutes, and disappeared after defecation. 44 days after completion: After dinner, there was right upper quadrant pain. 45 days after completion: The patient vomited once during the night. Afterward, abdominal pain lessened. There were no marked changes in blood test findings. 48 days after completion: Disappearance of gallstones was confirmed by abdominal echogram. The patient was discharged from the hospital. After discharge until the present, there has been no recurrence of cholelithiasis.	
	Concomitant medications: panipenem/betamipron, dexamethasone, glycerin, famotidine, dermal anti-inflammatory analgesic, miconazole				

Clinical Laboratory Values

	1 day before administration	On day 15 of administration	26 days after completion	33 days after completion	38 days after completion	44 days after completion
Total bilirubin (mg/dL)	--	--	0.7	0.7	0.6	0.4
Direct bilirubin (mg/dL)				0.2	0.2	
AST (GOT) (IU/L)	22	24	404	29	33	60
ALT (GPT) (IU/L)	12	20	208	28	23	17
Al-P (IU/L)	333	--	751	631	585	579
LDH (IU/L)	295	282	379	258	308	228
γ-GTP (IU/L)	--	17	238	132	110	79
Amylase (IU/L)	--	--	58	70	124	80
CRP (mg/dL)	17.60	0.00	0.11	0.01	0.03	0.00

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	
3	Male under age of 10	Pyogenic meningitis (none)	167 mg/kg 9 days	**Pancreatitis** Medical history: During about the past one and a half years, this drug was administered in high doses 13 times to treat meningitis. On day 1 of administration: Administration of this drug at 167 mg/kg/day (3.173 g/day) was started to treat pyogenic meningitis. On day 9 of administration (last day of administration): Administration of this drug was completed. 2 days after completion: The patient complained of abdominal pain, queasy, and vomiting at least once a day. 3 days after completion: The complaint of abdominal pain and vomiting increased in frequency. Intrabiliary debris, obstructive cholangitis, and pancreatitis developed. 6 days after completion: Abdominal pain intensified and vomiting increased in frequency to 5 to 6 times/day. 9 days after completion: The patient was examined at hospital as an out-patient. Worsening of hepatic function was suggested and the patient was hospitalized. [findings at time of hospitalization] There was no yellowing of skin or skin eruption. No head and neck, or heart and lungs abnormalities were confirmed. Abdominal wall was smooth and soft. There were no hepatosplenomegaly or abnormal masses on palpation. Due to strong spontaneous pain and tenderness of the right hypochondrium, and irradiating pain to the lower back, the patient was in the chest-knee position. [abdominal ultrasound test] Enlarged gallbladder and sandy debris within gallbladder accompanied by clear acoustic shadows were confirmed which shifted by a postural change, and floated in bile when vibration was applied to the abdominal wall.	Company report

				There were no clear abnormalities to hepatic parenchyma and intrahepatic bile duct, and the extrahepatic bile duct could not be visualized due to intestinal gas. It was diagnosed through test findings that the long-term administration of this drug at high and frequent doses caused the deposition of calcium salt within the gallbladder, resulting in obstructive cholangitis and pancreatitis during excretion. Ultrasound findings showed the deposition was fine sandy debris, and as natural excretion was expected, an antispastic and cholagogue were administered together with an infused load while the patient condition was observed. (symptomatic therapy) glutathione, vitamin C, vitamin B_1, vitamin B_2, scopolamine butylbromide, cefoperazone sodium, gabexate mesilate, 5% TZ (glucose), and ursodeoxycholic acid were administered. 10 days after completion: Almost all clinical symptoms disappeared and there was marked improvement in blood test findings. 12 days after completion: Abdominal ultrasound confirmed decreased intrabiliary debris. 13 days after completion: Amylase and total bilirubin levels normalized. 18 days after termination: Decreased intrabiliary debris was adhering to the gallbladder wall. 39 days after termination: Disappearance of intrabiliary debris was confirmed by abdominal ultrasound.	
	Concomitant medications: none				

Clinical Laboratory Values

	On day 1 of administration	9 days after completion	10 days after completion	11 days after completion	13 days after completion	15 days after completion
Total bilirubin (mg/dL)	--	1.3	0.8	0.9	0.5	0.7
Direct bilirubin (mg/dL)		0.8	0.3	0.3	0.1	0.1
AST (GOT) (IU/L)	20	574	197	74	14	12
ALT (GPT) (IU/L)	18	655	459	312	108	63
Al-P (IU/L)	--	47.7	47.2	45.5	32.0	30.9
LDH (IU/L)	287	411	338	258	181	203
γ-GTP (IU/L)	--	130	118	111	73	58
LAP (IU/L)	--	542	519	495	331	300
Lipase (IU/L)	--	5370	878	204	171	78
Amylase (IU/L)	--	2965	1085	290	166	159
Urine amylase (IU/L)	--	23380	--	--	487	487
CRP (mg/dL)	--	0.3	--	--	--	--

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
LAP: Leucine Aminopeptidase
CRP: C-Reactive Protein

3 Adsorbed Diphtheria-Purified Pertussis-Tetanus Combined Vaccine

Brand Name (name of company)	DPT "KAKETSUKEN" Syringe (The Chemo-Sero-Therapeutic Research Institute) Adsorbed Diphtheria-purified Pertussis-Tetanus Combined Vaccine (Denka Seiken Co., Ltd.) Adsorbed Diphtheria-purified Pertussis-Tetanus Combined Vaccine (The Chemo-Sero-Therapeutic Research Institute) Adsorbed Diphtheria-purified Pertussis-Tetanus Combined Vaccine "S Hokken" (The Kitasato Institute) Adsorbed Diphtheria-purified Pertussis-Tetanus Combined Vaccine "BIKEN" (Research Institute for Microbial Diseases, Osaka University) Adsorbed Diphtheria-purified Pertussis-Tetanus Combined Vaccine Kit "Takeda" (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Mixed biological preparations
Indications	This drug is used for the prevention of pertussis, diphtheria, and tetanus.

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

[Adverse reactions (clinically significant adverse reactions)]	**Encephalopathy**: Encephalopathy may occur. After vaccination, symptoms such as pyrexia, quadriplegia, convulsion, and consciousness disturbed occur. If this disease is suspected, MRI diagnosis etc. should be conducted and appropriate measures should be taken. **Convulsions:** Convulsions may occur. Ordinarily symptoms of convulsion occur immediately after vaccination to a few days after vaccination. If this disease is suspected, patients should be carefully monitored, 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 under age of 10	Prevention of pertussis, diphtheria, and tetanus (none)	0.5 mL once	**Acute encephalopathy** On day 1 of vaccination The patient was vaccinated with this drug (additional vaccination for stage I). 3 days after vaccination: Attack lasting under a minute with eyeball fixation and loss of consciousness developed. 5 days after vaccination: Similar attack occurred. 7 days after vaccination: Similar attack occurred. From this day, the patient lost vigor during the interval in between attacks and did not speak. Altered state of consciousness was surmised. 11 days after vaccination: Similar attacks occur multiple times. θ wave burst was confirmed during attack through electroencephalogram. The patient was hospitalized. She was clinically asymptomatic. Test results: Cerebrospinal fluid cell count: 3/3. Circulating antibodies: PT 3 EU/mL, FHA 89 EU/mL.	Company report

				Cerebrospinal fluid antibodies: PT<1 EU/mL, FHA<1 EU/mL. Electroencephalogram confirmed divergence in left/ right θ waves at the onset of sleep. Both head CT and head MRI did not indicate abnormal findings. 21 days after vaccination: The symptoms improved.	
	Concomitant medications: none				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male under age of 1	Prevention of pertussis, diphtheria, and tetanus (none)	0.5 mL once	**Status epilepticus, pyrexia** On day 1 of vaccination: The patient was vaccinated with this drug in the morning. 38°C level pyrexia developed from the evening. 1 day after vaccination: Pyrexia rose to 40°C. Cefditoren pivoxil and acetaminophen were prescribed and condition was observed. Convulsion occurred. (generalized chronic convulsion) The patient was transported to hospital by ambulance. Convulsions persisted after arrival. After securing an intravenous line, convulsions continued despite two set of administrations of diazepam administration at 3 mg (iv). Convulsions resolved through administration of approximately 25 mg of phenytoin sodium (iv). 7 day after vaccination: Symptoms improved and the patient was discharged from the hospital.	Company report
	Concomitant medications: none				

4 Torasemide

Brand Name (name of company)	Luprac Tablets 4 mg and 8 mg (Mitsubishi Pharma Corporation)
Therapeutic Category	Diuretics
Indications	Cardiac edema, renal edema, hepatic edema

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder with increased AST (GOT), ALT (GPT) and Al-P levels, etc. or jaundice may occur. Patients should be carefully monitored, and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Hypokalaemia, hyperkalaemia: Hypokalaemia or hyperkalaemia may occur. Arrhythmia, general malaise and weakness, etc. may occur with abnormal change in serum potassium level. If abnormalities 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	Male 50s	Chronic cardiac failure (none)	4 mg 6 days	**Hepatic function disorder** On day 1 of administration: Administration of this drug was started as a diuretic supplement. On day 3 of administration: Increased anorexia and decreased hepatic function were confirmed (elevation of leaking enzymes). On day 5 of administration: Hepatic function disorder developed. On day 6 of administration (day of discontinuation): Administration of this drug was discontinued. Thereafter, test values and symptoms gradually diminished. 11 days after discontinuation: The test values were normalized. Treatment drug: glycyrrhizin/glycine/cysteine (intravenous injection)	Company report
	Concomitant medications: aspirin, ranitidine hydrochloride, furosemide, spironolactone, allopurinol, zopiclone				

Clinical Laboratory Values

	1 day before administration	On day 6 of administration (day of discontinuation)	11 days after discontinuation
AST (GOT) (IU/L)	31	972	40
ALT (GPT) (IU/L)	29	589	82
LDH (IU/L)	567	2820	448
Total bilirubin (mg/dL)	1.5	3.3	1.5

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 70s	Cardiac failure (hypertension, gout)	8 mg 20 days ↓ 4 mg 8 days	**Hypokalaemia** The primary disease was angina pectoris and myocardial infarction old. On day 1 of administration: Administration of this drug was started to treat cardiac failure. On day 4 of administration: K value was 4.0 mEq/L. On day 21 of administration: K value was 2.8 mEq/L. Dosage of this drug decreased to 4 mg from 8 mg. Spironolactone 0.5 tablets and potassium chloride 2400 mg were added. On day 28 of administration (day of discontinuation): K value restored to 4.3 mEq/L. Administration of this drug and potassium chloride was discontinued. 1 tablet of furosemide was added.	Company report
	Concomitant medications: carvedilol, efonidipine hydrochloride, mexiletine hydrochloride				

Clinical Laboratory Values

	16 days before administration	1 day before administration	On day 4 of administration	On day 8 of administration	On day 11 of administration	On day 13 of administration	On day 21 of administration	On day 28 of administration (day of discontinuation)	14 days after discontinuation
Na (mEq/L)	145	136	140	138	140	136	143	138	139
K (mEq/L)	3.4	4.6	4.0	3.9	4.7	3.5	2.8	4.3	3.9
Cl (mEq/L)	106	100	104	103	103	96	105	103	105
BUN (mg/dL)	17	26	31	31	28	36	16	16	26
Creatinine (mg/dL)	1.75	1.37	1.35	1.39	1.24	2.07	1.48	1.41	1.81

Na: Sodium
K: Potassium
Cl: Chloride
BUN: Blood Urea Nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 70s	Cardiac failure (none)	4 mg 27 days	**Hyperkalaemia, bradycardia** The primary disease was diabetes mellitus, myocardial infarction (post coronary bypass surgery), and hypothyroidism. 1 day before administration: Administration of candesartan cilexetil was started to treat cardiac failure. On day 1 of administration: Administration of this drug and spironolactone was started to treat cardiac failure. On day 27 of administration (day of discontinuation): The patient was emergently hospitalized due to vomiting, bradycardia, and hyperkalaemia (K value: 7.7 mEq/L). Photophobia and sinus bradycardia was confirmed through electrocardiogram. Heart rate was 38 bpm. Administration of this drug and spironolactone was discontinued. After intravenous injections of 1 ampule of calcium gluconate and 2 ampules of sodium bicarbonate, and oral administration of 10 g of calcium polystyrene sulfonate, improvement of bradycardia was confirmed through electrocardiogram. Heart rate increased to 70 bpm. 2 days after discontinuation: As K value returned to 4.7 mEq/L, the patient was discharged from the hospital.	Company report
	Concomitant medications: candesartan cilexetil (suspected drug), spironolactone (suspected drug), ticlopidine hydrochloride, isosorbide mononitrate, diltiazem hydrochloride, atorvastatin calcium, aspirin/dialuminate, nitroglycerin, famotidine, magnesium oxide, sennoside, insulin human (Genetical recombination), carvedilol				

Clinical Laboratory Values

	2 days before administration	On day 3 of administration	On day 10 of administration	On day 27 of administration (day of discontinuation)		1 day after discontinuation	2 days after discontinuation	9 days after discontinuation
				At onset	After improvement			
Heart rate (bpm)	--	76	--	38	70	--	--	--
Na (mEq/L)	140	137	138	136		138	140	141
K (mEq/L)	4.4	4.6	5.0	7.7		5.2	4.7	4.5
Cl (mEq/L)	107	106	105	105		104	103	102
BUN (mg/dL)	23	35	30	40		28	28	31
Creatinine (mg/dL)	1.1	1.3	1.3	1.2		1.2	1.3	1.1

Na: Sodium
K: Potassium
Cl: Chloride
BUN: Blood Urea Nitrogen

5 Japanese Encephalitis Vaccine

Brand Name (name of company)	Japanese Encephalitis "KAKETSUKEN" Syringe (The Chemo-Sero-Therapeutic Research Institute) Japanese Encephalitis Vaccine "KAKETSUKEN" N (The Chemo-Sero-Therapeutic Research Institute) Japanese Encephalitis Vaccine "S Hokken" (The Kitasato Institute) Japanese Encephalitis Vaccine "Seiken" (Denka Seiken Co., Ltd.) Japanese Encephalitis Vaccine "BIKEN" (Research Institute for Microbial Diseases, Osaka University) Japanese Encephalitis Vaccine Kit "Takeda" (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Vaccines
Indications	This drug is used for the prevention of Japanese encephalitis.

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

[Adverse reactions (clinically significant adverse reactions)]

Idiopathic thrombocytopenic purpura: Idiopathic thrombocytopenic purpura may occur. Ordinarily, purpura, epistaxis, oral mucosa bleeding etc. may occur from a few days to about 3 weeks after vaccination. If this disease is suspected, patients should be carefully monitored through blood tests etc., and appropriate measures should be taken.

Encephalopathy: Encephalopathy may occur. After vaccination, symptoms such as pyrexia, quadriplegia, convulsion, and consciousness disturbed occur. If this disease is suspected, MRI diagnosis etc. should be conducted and appropriate measures should be taken.

Convulsions: Convulsions may occur. Ordinarily symptoms of convulsion occur immediately after vaccination to a few days after vaccination. If this disease is suspected, patients should be carefully observed, 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	Male under age of 10	Prevention of Japanese encephalitis (none)	0.5 mL once	**Idiopathic thrombocytopenic purpura (ITP)** On day 1 of vaccination: The patient was vaccinated with this preparation (2nd vaccination). 20 days after vaccination: As epistaxis did not stop for about 30 minutes early in the morning, the patient was examined at a nearby otolaryngologist. But apart from mild injury to the nasal mucosa, no particular problems were found. 21 days after vaccination: Concerned about the above episode, the patient visited pediatrician with his parents and examined as an outpatient. Multiple purpura on legs and torso were confirmed through physical examinations (mother was concerned that internal bleeding was not healing easily). Moreover, during this period for about 1 month, common cold-like symptoms were not observed. As blood test confirmed a decreased platelet count of $2.9 \times 10^4/mm^3$, ITP was suspected.	Company report

				The patient was emergently hospitalized and treated with bed rest. As the result of blood coagulation test, no abnormalities were confirmed. The patient was hospitalized for 8 days. 23 days after vaccination: Bone marrow aspiration was performed. Nuclear cell count was $25.7 \times 10^4/mm^3$, megakaryocytes was $203/mm^3$. (with large number of small basophilic cells) Blast cells and which suggest malignancy were not confirmed and the patient was diagnosed with ITP. IV drip infusion of human normal immunoglobulin at 6g was started. Test results of circulating antibody levels: Rubella IgG 27.8, rubella IgM 0.09, Japanese encephalitis 80, platelet-associated antibodies PAIgG 60.0. 24 days after vaccination: Platelet count increased to $13.4 \times 10^4/mm^3$. Haemorrhage or splenomegaly was not confirmed through echogram conducted to detect intra-abdominal lesions such as in the spleen etc. 25 days after vaccination: Platelet count increased to $23.9 \times 10^4/mm^3$. As purpura on the lower limbs; and torso markedly decreased, IV drip infusion of human normal immunoglobulin was discontinued after 3 consecutive days treatment. 28 days after vaccination: Thereafter, platelet count steadily increased, and as purpura showed decreasing tendency and improved, the patient was discharged from the hospital. (This child received vaccination for rubella about 11 months before).	
	Concomitant medications: none				

Clinical Laboratory Values

	21 days after vaccination	23 days after vaccination	24 days after vaccination	25 days after vaccination	28 days after vaccination
PLT ($\times 10^4/mm^3$)	2.9	6.4	13.4	23.9	37.7

PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female under age of 10	Prevention of Japanese encephalitis (none)	0.5 mL once	**Convulsions** On day 1 of vaccination: The patient was vaccinated with this preparation. Approx. 1 hour and 30 minutes after vaccination: The patient's father noticed that there was something wrong with the appearance of the patient's eyes. Approx. 2 hours after vaccination: The patient was examined at a medical institution. Approx. 2 hours and 30 minutes after vaccination: Eyeball fixation to upper left developed. Depressed level of consciousness was noted (JCS200-300). Intravenous line for IV drip was secured, 200 mg of hydrocortisone sodium succinate and oxygen at 4 L/minute were administered.	Company report

				Approx. 3 hours after vaccination: Twitching of left arm developed. 1 mg of diazepam was intravenously injected. Twitching subsided after about 3 minutes. As consciousness disturbed continued thereafter, the patient was emergently transported to another medical institution. Approx. 3 hours and 30 minutes after vaccination: At time of arrival to hospital, body temperature, pulse rate, and blood pressure, 36.8°C, 112 bpm, and 132/60 mmHg, respectively. JCS was III-100. Chills developed. The patient cried violently when she was touched. No abnormalities were found through blood test and head CT. Approx. 6 hours after vaccination: The patient awoke. There was no consciousness disturbed. No abnormal neurologic findings were confirmed. The patient had no pyrexia. No abnormal findings were confirmed by cerebrospinal fluid test. 60 mg of phenobarbital sodium suppository was administered. Administration of concentrated glycerin/fructose 5 mL/kg × 3 times/day and IV drip of aciclovir 10 mg/kg × 3 times/day was started. 1 day after vaccination: No abnormal findings were confirmed from head MRI and electroencephalogram. Thereafter, the patient had no pyrexia and general condition was good. Administration of concentrated glycerin/fructose was discontinued. 2 days after vaccination: No abnormal findings were confirmed by blood test. Administration of Zovirax was discontinued. 3 days after vaccination: IV drip line was removed. 4 days after vaccination: Electroencephalogram was re-performed but there were no abnormal findings. 5 days after vaccination: The patient was recovered from convulsions and consciousness disturbed. The patient was discharged from the hospital.	
	Concomitant medications: none				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female under age of 10	Prevention of Japanese encephalitis (none)	0.5 mL once	**Acute encephalopathy** 23 days before vaccination: The patient received the first vaccination of this preparation at the 1st stage. On day 1 of vaccination: The patient received the second vaccination of this preparation at the 1st stage. 7 days after vaccination: Pyrexia and consciousness disturbed were confirmed. The patient was hospitalized. Improvement and aggravation of consciousness disturbed were repeated. No abnormal findings were observed from head MRI. Numerous θ waves were confirmed by electroencephalogram even during her waking hours. <clinical laboratory values> White blood cell count was 21300/mm^3 13 days after vaccination: Although consciousness disturbed showed improvement tendency, there were fluctuations. The patient's consciousness level had not returned to the levels before the onset of symptoms. <clinical laboratory values> Viral isolation test Test materials: Feces, pharyngeal swab (11 days after vaccination), cerebrospinal fluid (11 days after vaccination) Test results: Viral isolation was negative with HEF.HEp-2.Vero.MDCK.RD_{18s}.GMK. Japanese encephalitis virus neutralizing antibody level measurement test Collection date of test materials: 10 days after vaccination Test results: Serum Nakayama strain 2.98 (10^n) Beijing strain 4.47 Cerebrospinal fluid Nakayama strain <1.0 Beijing strain 1.60	Company report
	Concomitant medications: none				

3

Revision of PRECAUTIONS

(No. 165)

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 bulletin before previous one (Pharmaceuticals and Medical Devices Safety Information No. 211) (excluding those presented in "2. Important Safety Information" of this Bulletin), together with reference materials.

1 <Ophthalmic agents>
Fradiomycin Sulfate/Methylprednisolone Betamethasone Sodium Phosphate/Fradiomycin Sulfate (ophthalmic ointment)

[Brand Name]	Neo-Medrol EE Ointment (Sumitomo Pharmaceuticals Co., Ltd.), Rinderon-A Ointment for Eye and Ear (Shionogi & Co., Ltd.)
[Contraindications]	Using this drug in the inner ear for patients with perforation of ear drum.
[Careful Administration]	"Patients with perforation of ear drum" was omitted.
<Reference Information>	Company report

2 <Antihypertensives>
Olmesartan Medoxomil

[Brand Name]	Olmetec Tablets 10 mg and 20 mg (Sankyo Co., Ltd.)
[Clinically Significant Adverse Reactions (similar drug)]	**Hypoglycaemia:** Since hypoglycemia may occur from the use of other angiotensin II receptor antagonists (patients being treated for diabetes mellitus are more susceptible), patient should be carefully monitored. If feeling of weakness or hungry, cold sweat, tremor of hands, decreased mental concentration, convulsions, disturbed consciousness, etc. are observed, administration should be discontinued, and appropriate measures shoud be taken.
<Reference Information>	Company report

3 <Digestive organ agents-Miscellaneous>
Infliximab (Genetical recombination)

[Brand Name]	Remicade for I.V. Infusion 100 (Tanabe Seiyaku Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder:** Hepatic function disorder with significant elevation of AST (GOT), ALT (GPT), γ-GTP levels etc. may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures. Concomitant use of immunosuppressive therapy may reactivate hepatitis B virus in patients who are carriers of this virus (HBs antigen positive).
<Reference Information>	Company report

4 <Hemorrhoidal preparations> Tribenoside

[Brand Name] Hemocuron (Amato Pharmaceutical Products, Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Erythema (exudativum) multiforme:** Erythema multiforme (exudativum) may occur. Patients should be carefully monitored and if any abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

5 <Dermatological antimicrobial agents> Iodoform

[Brand Name] Tamagawa Iodoform Gauze (Tamagawa Eizai Co., Ltd.) Hakuzo Iodoform Gauze (Hakuzo Medical Technos Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)]

Iodism

Iodism with the following symptoms may occur. Patients should be carefully monitored through measurement of total blood iodine concentration, etc. If abnormalities are observed, discontinue use, wash the area thoroughly, and take appropriate measures.

1) Psychoneurotic: excitement, delirium, unrest, orientation disturbed, memory impairment, blues, coma, syncope, somnolence, sleep loss (sleep disorder), etc.
2) Digestive organ: anorexia, etc.
3) Others: headache, general malaise, tachycardia, etc.

<Reference Information> Company report

6 <Analgesics, anti-itchings, astringents, anti-inflammatory agents> Betamethasone Valerate/Fradiomycin Sulfate

[Brand Name] Betnevate N Ointment, Betnevate N Cream (GlaxoSmithKline K.K.), and others

[Contraindications] Using this drug in the inner ear for patients with perforation of ear drum.

<Reference Information> Company report

7 <Miscellaneous metabolism agents> Azathioprine

[Brand Name] Azanin Tablets (Tanabe Seiyaku Co., Ltd.), Imuran Tablets (GlaxoSmithKline K.K.)

[Important Precautions]

Infectoin with varicella or shingles may become severe during the administration of this drug. The following cautions should be exercised:

1) Before starting the administration of this drug, the prescriber should check to see if the patient has a medical history of varicella or shingles and vaccination history. Serologic testing of viral antibody levels may be useful in determining previous exposure.
2) Patients who have no history of varicella or shingles should be carefully monitored and care should be taken at all times to prevent infection of varicella or shingles. If the patient is suspected of infection or has become infected, the patient should be instructed to seek immediate medical examination and to conduct appropriate measures such as immunoglobulin administration etc.
3) Caution should be exercised even for patients with a medical history of varicella or shingles and past vaccination as the onset of varicella or shingles is still possible during the administration of this drug.

In case of concomitant use of other immunosuppressive therapy, increased sensitivity toward infection and the onset of lymphoma and other malignant tumors may occur due to excessive immune suppression. Caution should be

exercised to keep the minimum effective immunosuppression, etc. Moreover, there have been reports that non-Hodgkin lymphoma and Kaposi sarcoma has regressed (involuted) through reduction or discontinuation of immunosuppressive agents.

[Adverse Reactions (clinically significant adverse reactions)] Neoplasm malignant (lymphoma, skin cancer, sarcoma, cervical cancer, acute myeloid leukaemia, myelodysplastic syndrome etc.)

<Reference Information> Company report

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8 <Antineoplastics-Miscellaneous> Gefitinib

[Brand Name] Iressa Tablets 250 (AstraZeneca K.K.)

[Important Precautions] Physicians should be referred to the latest information such as "Guidelines for Gefitinib Use" etc. issued by the Japan Lung Cancer Society at the administration of this drug.

[Other Precautions] In a double-blind, placebo-controlled parallel-group phase III trial randomized patients with recurrent or advanced non-small cell lung cancer (NSCLC) who had received 1 or 2 prior chemotherapy conducted overseas, although a statistically significant difference was confirmed in cytoreductive effect, a statistical significant difference was not confirmed in prolonged survival time among all targeted patients (HR = 0.89, p = .09, median 5.6 months vs 5.1 months) and in the adenocarcinoma patient group (HR = 0.84, p = .09, median 6.3 months vs 5.4 months).

<Reference Information> Company report

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9 <Kampo medicines> Saikokeishikankyoto

[Brand Name] TSUMURA Saikokeishikankyoto Extract Granules for Ethical Use (Tsumura & Co.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic dysfunction and jaundice:** Hepatic dysfunction and/or jaundice with marked elevation of AST (GOT), ALT (GPT), Al-P and γ-GTP or other symptoms may occur. The patient 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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10 <Kampo medicines> Sammotsuogonto

[Brand Name] TSUMURA Sammotsuogonto Extract Granules for Ethical Use (Tsumura & Co.)

[Adverse Reactions (clinically significant adverse reactions)] **Interstitial pneumonia:** If pyrexia, cough, dyspnoea, abnormal pulmonary sound (fine crackle), etc. are observed, administration of this product should be discontinued, and examinations such as chest X-ray should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken. Besides, the patient should be advised to discontinue this product immediately and to make contact with the physician in the event of pyrexia, cough, dyspnoea, etc.
Hepatic function disorder, jaundice: Hepatic dysfunction and/or jaundice with marked elevation of AST (GOT), ALT (GPT), Al-P and γ-GTP or other symptoms may occur. The patient 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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11 <Kampo medicines> Boiogito

[Brand Name] TSUMURA Boiogito Extract Granules for Ethical Use (Tsumura & Co.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Interstitial pneumonia:** If pyrexia, cough, dyspnoea, abnormal pulmonary sound (fine crackle), etc. are observed, administration of this product should be discontinued, and examinations such as chest X-ray should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken. Besides, the patient should be advised to discontinue this product immediately and to make contact with the physician in the event of pyrexia, cough, dyspnoea, etc.

<Reference Information> Company report

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12 <Kampo medicines> Rikkunshito

[Brand Name] TSUMURA Rikkunshito Extract Granules for Ethical Use (Tsumura & Co.), and others

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic dysfunction and jaundice:** Hepatic dysfunction and/or jaundice with marked elevation of AST (GOT), ALT (GPT), Al-P and γ-GTP or other symptoms may occur. The patient 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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13 <Antivirals> Tenofovir Disoproxil Fumarate

[Brand Name] Viread Tab. 300 mg (Japan Tobacco Inc.)

[Warning]

WARNING

Reactivation of chronic hepatitis B may occur by discontinuation of administration in patients complicated with chronic hepatitis B. Extra caution should be exercised when discontinuing administration of this drug. Caution should be exercised as the disease may become serious especially when decompensated.

[Important Precautions] "This drug is not indicated for the treatment of chronic hepatitis B and its efficacy and safety has not been established. There have been reports that chronic hepatitis B has become aggravated after discontinuation of administration in patients complicated with chronic hepatitis B.
When administration is discontinued in such patients, patients should be monitored by taking clinical symptoms and clinical laboratory values even after discontinuation." was omitted.

Redistribution/accumulation of body fat may occur following the use of anti-HIV drugs. If any such abnormality is noted, appropriate measures should be taken.

Immune reconstitution syndrome has been reported in patients under anti-HIV multidrug therapy including this drug. After the start of treatment, inflammatory reactions not only to symptomatic but also to asymptomatic opportunistic infections (e.g., caused by Mycobacterium avium complex, cytomegalovirus, and Pneumocystis) may develop following restoration of immune function. These inflammatory reactions, therefore, should be appraised and, as deemed necessary, appropriate therapy should be considered.

<Reference Information> Company report

14 <Biological preparations-Miscellaneous> Peginterferon Alfa-2a (Genetical recombination)

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

[Important Precautions] Neutropenia, platelets decreased, and anaemia may occur. Blood tests should be conducted at least twice a week for the first week after starting administration. Thereafter, conduct tests immediately prior to each dosing, as well as regular tests after each administration until test values normalize. Moreover, as hepatic and renal disorder may occur, conduct regular biochemical tests every 4 weeks.

<Reference Information> Company report

15 <Synthetic narcotics> Fentanyl Citrate

[Brand Name] Fentanest Injection (Sankyo Co., Ltd.)

[Warning]

WARNING

The epidural and subarachnoid administration of this drug should only be a conducted by a physician well experienced in these administration methods and only toward patients judged to be suitable candidates for this drug.

[Contraindications]

Patients (subarachnoid administration) with central nervous system disease (meningitis, poliomyelitis, tabes dorsalis etc.)
Patients (subarachnoid administration) with an active disease such as tuberculosis of the spinal cord/spine, spondylitis, and metastatic tumor etc.

[Careful Administration] Patients (contraindication: epidural administration, subarachnoid administration) with a central nervous system disease (meningitis, poliomyelitis, tabes dorsalis etc.)
Patients (contraindication: epidural administration, subarachnoid administration) with an active disease such as tuberculosis of the spinal cord/spine, spondylitis and metastatic tumor etc.

<Reference Information> Company report

16 Over the counter drugs Saikokeishikankyoto

[Brand Name] Saikokeishikankyoto Extract Granules (Kanebo, 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 a case.

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

<Reference Information> Company report

17 Over the counter drugs Sammotsuogonto

[Brand Name] Sammotsuogonto Extract Granules KM (Kahya Co., Ltd.)

[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 a case.

Interstitial pneumonia: Shortness of breath, dyspnoea, and pyrexia, etc. accompanying cough may occur.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

<Reference Information> Company report

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18 Over the counter drugs
Boiogito

[Brand Name] TSUMURA Kampo Boiogito Extract Granules (Tsumura & Co.), and others

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for a consultation.
If the following symptoms are observed after taking this drug
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.
Interstitial pneumonia: Shortness of breath, dyspnoea, and pyrexia, etc. accompanying cough may occur.

<Reference Information> Company report

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19 Over the counter drugs
Rikkunshito [containing daily maximum amount of glycyrrhiza no less than 1g (extract containing raw herbs no less than 1 g)]

[Brand Name] Rikkunshito Extract Granules (Kanebo, Ltd.), and others

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for a consultation.
If the following symptoms are observed after taking this drug:
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

<Reference Information> Company report

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20 Over the counter drugs
Rikkunshito [containing daily maximum amount of glycyrrhiza no less than 1g (extract containing raw herbs no more than 1 g)]

[Brand Name] TSUMURA Kampo Rikkunshito Extract Granules (Tsumura & Co.), and others

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for a consultation.
If the following symptoms are observed after taking this drug
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

<Reference Information> Company report

4

List of products subject to Early Post-marketing Phase Vigilance

(As of May 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Valganciclovir Hydrochloride / Valixa Tablets 450 mg	Tanabe Seiyaku Co., Ltd.	November 5, 2004
Pamidronate Disodium / Aredia Injection 15 mg and 30 mg*[1]	Nihon Ciba-Geigy K.K.	November 29, 2004
Adefovir Pivoxil / Hepsera Tablets 10	GlaxoSmithKline K.K.	December 8, 2004
Arsenic Trioxide / Trisenox Injection 10 mg	Nippon Shinyaku Co., Ltd.	December 8, 2004
Peginterferon Alfa-2b (Genetical recombination) / PegIntron Sterile Powder for Injection 50 μg, 100 μg, and 150 μg	Schering-Plough K.K.	December 8, 2004
Lamivudine / Zefix Tablets 100*[2]	GlaxoSmithKline K.K.	December 8, 2004
Ribavirin / Rebetol Capsules 200 mg*[3]	Schering-Plough K.K.	December 8, 2004
Tiotropium Bromide Hydrate / Spiriva Inhalation Capsules 18 μg	Nippon Boehringer Ingelheim Co., Ltd.	December 10, 2004
Fosamprenavir Calcium Hydrate / Lexiva Tablets 700	GlaxoSmithKline K.K.	January 7, 2005
Zoledronic Acid Hydrate / Zometa Injection 4 mg	Nihon Ciba-Geigy K.K.	January 21, 2005
Beclometasone Dipropionate / Qvar Aerosol 50 and 100*[4]	Dainippon Pharmaceutical Co., Ltd.	January 19, 2005
Pralmorelin Hydrochloride / Ghrp Kaken 100 for Injection	Kaken Pharmaceutical Co., Ltd.	February 25, 2005
Aluminum Potassium Sulfate/Tannic Acid / Zione Injection/Lidocaine, Zione Injection	Mitsubishi Pharma Corporation	March 15, 2005
Epinastine Hydrochloride / Alesion Dry Syrup 1%	Nippon Boehringer Ingelheim Co., Ltd.	March 23, 2005
Etanercept (Genetical recombination) / Enbrel 25 mg for s.c. Injection	Wyeth K.K.	March 30, 2005
Oxaliplatin / Elplat for Injection 100 mg	Yakult Honsha Co., Ltd.	April 6, 2005
Tacrolimus Hydrate / Prograf 0.5 mg and 1 mg*[5]	Astellas Pharma Inc.	April 11, 2005

Emtricitabine Emtriva Capsules 200 mg	Japan Tobacco Inc.	April 19, 2005
Emtricitabine/Tenofovir Disoproxil Fumarate Truvada Tablets	Japan Tobacco Inc.	April 19, 2005

Note) Subject to additional indication etc.

*1: An additional indication for "osteolytic bone metastasis in breast cancer"

*2: An additional indication for "in the case of concurrent use with adefovir pivoxil"

*3: An additional indication for "improvement of viraemia in the following chronic hepatitis C cases through concomitant use with peginterferon alfa-2b (Genetical recombination)"

*4: Additional indications of pediatric dosage "In children, 50 μg of the drug is generally inhaled into the mouth twice a day. Moreover, although the dosage may be increased/decreased as needed according to age and symptoms, the maximum daily dosage is 800 μg in adults and 200 μg in children. (underlined parts are additions)"

*5: An additional indication for "Rheumatoid arthritis (only for cases which are not adequately responsive to conventional therapies"