

# Pharmaceuticals and Medical Devices Safety Information

No. 214 June 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).

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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).*

## 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. 213).

### 1 Alprostadil, Alprostadil Alfadex (20 µg injectable dosage form)

<b>Brand Name (name of company)</b>	<b>Alprostadil</b> Alyprost Injection (Fuji Pharma Co., Ltd.) Palux Inj. 5 µg and 10 µg (Taisho Pharmaceutical Co., Ltd.) Prink Inj. 5 µg and 10 µg, Prink Inj. Syringe 5 µg and 10 µg (Taiyo Yakuhin Co., Ltd.) Liple Injection 5 µg and 10 µg (Mitsubishi Pharma Corporation) <b>Alprostadil Alfadex (20 µg injectable dosage form)</b> Tandetron Inj. (Takata Seiyaku Co., Ltd.) Apistandin for Injection (Fuji Pharma Co., Ltd.) Altesil 20 for Injection (Taiyo Yakuhin Co., Ltd.) Ipuseriru for Injection (Tobishi Pharmaceutical Co., Ltd.) Prostandin for Injection (Ono Pharmaceutical Co., Ltd.) Mediprost for Inj. (Sankyo Yell Yakuhin Co., Ltd.)
<b>Therapeutic Category</b>	Cardiovascular agents-Miscellaneous
<b>Indications</b>	<b>Alprostadil</b> <input type="radio"/> Improvement of ulcers of extremities and resting pains in chronic arterial occlusion (Buerger's disease and atherosclerosis obliterans) <input type="radio"/> Improvement of skin ulcers in the following diseases: Progressive systemic sclerosis Systemic lupus erythematosus <input type="radio"/> Improvement of skin ulcers in diabetes mellitus <input type="radio"/> Improvement of subjective symptoms resulting from peripheral circulation disturbance and recovery from disturbance of peripheral circulation, nerve or motor function in vibration disease <input type="radio"/> Patency of ductus arteriosus in ductus arteriosus dependent congenital heart disease <input type="radio"/> Improvement of contrast in superior mesenteric arterial portography (only Palux Inj. 5 µg and 10 µg, Liple Injection 5 µg and 10 µg) <b>Alprostadil Alfadex (20 µg injectable dosage form)</b> I. Intra-arterial administration Improvement of ulcer in the extremities and resting pain in chronic arterial occlusive disease (Buerger's disease and arteriosclerosis obliterans) II. Intravenous administration 1. Improvement of subjective symptoms and recovery from peripheral circulatory, nervous and motor function disorder associated with peripheral vascular disturbance in vibration disease 2. Maintenance of blood flow following vascular reconstructive surgery 3. Improvement of ulcer in the extremities and resting pain in chronic arterial occlusive disease (Buerger's disease and arteriosclerosis obliterans) where intra-arterial administration is judged to be inadequate 4. Patency of ductus arteriosus in ductus arteriosus-dependent congenital heart disease (only Tandetron Inj., Altesil 20 for Injection, Prostandin for Injection)

<<PRECAUTIONS (underlined parts are additions)>>

[Adverse Reactions (clinically significant adverse reactions)]

**Myocardial infarction:** Myocardial infarction may occur. Patients should be carefully monitored. If chest pain, sensation of chest pressure, or electrocardiogram abnormal is 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 80s	Arteriosclerosis obliterans (diabetes mellitus)	60 µg 1 day ↓ 120 µg 7 days	<p><b>Acute myocardial infarction</b></p> <p>Approx. 11 years before administration: The patient was diagnosed with diabetes mellitus which was controlled relatively well with oral therapeutics.</p> <p>11 days before administration: The patient experienced fell 3 days before and suffered contusion of the 5th right toe and was started on analgesic-antipyretic and antiinflammatory drug for treatment.</p> <p>6 days before administration: Small wound appeared on the tip of the right 5th toe. Arteriosclerosis obliterans was suspected and the administration of 100 mg of cilostazol and 1800 mg of ethyl icosapentate were started.</p> <p>On day 1 of administration: Enlargement of the wound and necrosis, psychralgia of the right foot were confirmed. The patient was hospitalized as dorsal artery of the right foot was impalpable and administration of 60 µg/2 hours of this drug was started. From the following day, 60 µg of this drug was administered twice a day. Abnormal T waves (anterior myocardial ischemia was suspected) and complete right bundle branch block were confirmed by electrocardiogram.</p> <p>On day 7 of administration: Necrosis was almost completely healed and pain in right foot improved.</p> <p>On day 8 of administration (day of discontinuation): At evening, blood pressure was 126/70 mmHg. 1 hour and 30 minutes later, during the second dosing of this drug through IV drip, respiratory discomfort and wheezing occurred followed by acute myocardial infarction. Oxygen mask at 2 L was started, nebulizer was implemented. Blood pressure was 126/70 mmHg. 2 hours later, as respiratory discomfort continued, instillation of diprophylline was performed. Abnormal Q waves (leads II, III, aVF) were confirmed by electrocardiogram. As respiratory discomfort continued, administration of this drug was discontinued and steroid was intravenously administered. As chest X-ray revealed pleural effusion in the right lung and increase in CTR, furosemide was intravenously injected. The volume of oxygen was increased to 5 L.</p>	Company report

				<p>Approximately 3 hours and 30 minutes later, as there was no change in respiratory discomfort, 0.5 mg of epinephrine was administered subcutaneously twice.</p> <p>1 day after discontinuation:  Late at night, respiratory discomfort and wheezing improved (SaO<sub>2</sub> 96%).  In the morning, as respiratory discomfort recurred, nebulizer was implemented.  Approximately 1 hour and 30 minutes later, furosemide was intravenously injected and nitroglycerin patch was applied.  In the afternoon, respiratory discomfort and wheezing was confirmed. As PaO<sub>2</sub> was 51.5 mmHg, oxygen was increased to 8 L.  Approximately 1 hour and 30 minutes later, abnormal Q waves (leads V<sub>1</sub>, III, aVF) were confirmed by electrocardiogram.  2 hours later, furosemide was intravenously injected, and respiratory discomfort had almost completely resolved after 7 hours.  Serious hypokinesia from the anterior wall to the septal area was confirmed by echocardiogram. EF was 40%.  Mild pleural effusion in the right lung was confirmed by chest X-ray.</p> <p>2 days after discontinuation:  Congestive symptoms in the lung field were found by chest X-ray.</p> <p>10 days after discontinuation:  Respiratory discomfort disappeared.</p> <p>23 days after discontinuation:  Although the patient recovered from acute myocardial infarction, cardiac function disturbance remained (Mild left ventricular enlargement and mild hypokinesia from the anterior wall to the septal area were found by echocardiogram. EF was 53%).</p>	
<p>Concomitant medications: brotizolam, acarbose, triazolam, pancreatic digestive enzyme, zaltoprofen, cilostazol, ethyl icosapentate, non-protein extract from cutaneous tissue of rabbit inoculated with vaccinia virus, glycyrrhizin/glycine/cysteine, sodium bicarbonate</p>					

### Clinical Laboratory Values

	On day 1 of administration	On day 8 of administration (day of discontinuation)	1 day after discontinuation	2 days after discontinuation	13 days after discontinuation
<b>WBC (/mm<sup>3</sup>)</b>	6890	7160	10490	8780	10270
<b>AST (GOT) (IU/L)</b>	13	40	176	87	13
<b>CK (CPK) (IU/L)</b>	--	216	970	483	73
<b>CRP (mg/dL)</b>	1.8	10.1	13.6	14.4	2.5
<b>BG (mg/dL)</b>	155	136	236	111	--
<b>Blood pressure (systolic) (mmHg)</b>	160	126	160	138	138
<b>Blood pressure (diastolic) (mmHg)</b>	80	70	66	82	72
<b>Blood gas</b>	<b>PaO<sub>2</sub> (mmHg)</b>	--	51.5	74.6	--
	<b>PaCO<sub>2</sub> (mmHg)</b>	--	27.2	34.5	--

WBC: White Blood Cell  
AST: Aspartate Aminotransferase  
CK: Creatine Kinase  
CRP: C-Reactive Protein

BG: Blood Glucose  
PaO<sub>2</sub>: Partial Pressure Arterial Oxygen  
PaCO<sub>2</sub>: Partial Pressure of Carbon Dioxide in Artery

## 2 Donepezil Hydrochloride

<b>Brand Name (name of company)</b>	Aricept Fine Granules 0.5%, Aricept Tablets 3 mg and 5 mg, Aricept D Tablets 3 mg and 5 mg (Eisai Co., Ltd.)
<b>Therapeutic Category</b>	Central nervous system agents-Miscellaneous
<b>Indications</b>	Suppression of progression of demential symptoms in mild to moderate dementia of the Alzheimer's type

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

#### [Adverse Reactions (clinically significant adverse reactions)]

**Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored, and if myalgia, feelings of weakness, CK (CPK) increased, myoglobin blood increased and myoglobin urine increased is observed, administration should be discontinued and appropriate measures should be taken. In addition, caution should be exercised against development of acute renal failure associated with rhabdomyolysis.

#### <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 70s	Alzheimer-type dementia (cerebral infarction, hyperuricaemia, hypertension, constipation, aneurysm, hyperlipidaemia, renal function disorder)	3 mg 12 days ↓ 5 mg 25 days	<p><b>Rhabdomyolysis</b></p> <p>38 days before administration: The patient was first examined at another hospital for sequelae of cerebral infarction and gastric cancer. Anorexia and dysphagia were noted. Renal function had also declined. (Cr: 1.51 mg/dL, red blood cell: <math>415 \times 10^4/\text{mm}^3</math>, haemoglobin: 11.9 g/dL, haematocrit: 41.0%)</p> <p>On day 1 of administration: Administration of 3 mg of this drug was initiated.</p> <p>On day 10 of administration: From around this time, the patient had difficulty in walking which gradually worsened.</p> <p>On day 13 of administration: Dosage of this drug was increased to 5 mg and continued.</p> <p>On day 24 of administration: From around this time, dysphagia worsened and that made swallowing difficult. The symptoms were gradually worsened thereafter.</p> <p>On day 37 of administration (day of discontinuation): Administration of the drug was discontinued.</p> <p>1 day after discontinuation: The patient was found slumped down into his wheelchair. He could no longer walk and was hospitalized in another hospital. At time of hospitalization, brown urine was observed. Examination on admission for infectious disease was not implemented.</p> <p>2 days after discontinuation: CK (CPK) value was significantly high at 126480 IU/L. Poor renal function at BUN 26.5 g/dL, Cr 2.8 mg/dL. As the patient was complicated with pneumonia, administration of piperacillin sodium at 2 g was started.</p>	Company report

				<p>Administrations of roxatidine acetate hydrochloride at 150 mg and methylprednisolone sodium succinate at 1000 mg were started.</p> <p>3 days after discontinuation: The patient was diagnosed with rhabdomyolysis based on BUN 51.4 mg/dL and Cr 4.93 mg/dL. CHDF (continuous haemodialysis filtration) was started from the same day. Antibiotic was administered. As renal function worsened, the patient was transferred to this hospital for dialysis etc. At the time of transfer, concomitant renal failure developed and the patient had hardly any micturition. Although dialysis etc. was started, there was onset of pneumonia, blood pressure decreased, and peripheral circulatory failure leading to necrosis of the right foot.</p> <p>As the patient developed multi-organ failure, and it was monitored over time.</p> <p>53 days after discontinuation: The patient died (cause of death: multi-organ failure).</p>	
Concomitant medications: aspirin, allopurinol, amlodipine besilate, doxazosin mesilate, magnesium oxide, sennoside					

### Clinical Laboratory Values

	38 days before admin.	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	5 days after discontinuation	7 days after discontinuation	9 days after discontinuation	35 days after discontinuation	45 days after discontinuation	50 days after discontinuation	53 days after discontinuation
<b>WBC (/mm<sup>3</sup>)</b>	--	16000	19100	22300	14500	15500	11200	15200	16000	12200	17700
<b>Neutrophils (%)</b>	--	96	94	90	94	98	94	--	--	--	--
<b>Eosinophils (%)</b>	--	0	0	0	0	0	0	--	--	--	--
<b>Basophils (%)</b>	--	0	0	0	0	0	0	--	--	--	--
<b>Monocytes (%)</b>	--	2	3	5	5	1	4	--	--	--	--
<b>Lymphocytes (%)</b>	--	2	3	5	1	1	2	--	--	--	--
<b>RBC (×10<sup>4</sup>/mm<sup>3</sup>)</b>	415	459	403	235	286	342	335				
<b>Haemoglobin (g/dL)</b>	11.9	12.7	11.5	6.8	8.5	10.1	10.0	7.8	7.9	7.6	8.0
<b>Haematocrit (%)</b>	41.0	39.1	34.7	21.0	24.1	29.9	30.1	22.0	21.1	20.6	21.6
<b>PLT (×10<sup>4</sup>/mm<sup>3</sup>)</b>	--	21.6	14.4	9.6	5.1	2.7	3.3	12.2	11.9	5.7	3.3
<b>AST (GOT) (IU/L)</b>		1233	946	409	2360	709	262	88	57	67	62
<b>ALT (GPT) (IU/L)</b>	--	306	333	220	843	566	302	35	75	95	93
<b>ALP (IU/L)</b>	--	--	470	317	319	388	291	--	--	--	--
<b>LDH (IU/L)</b>	--	--	2055	1315	2617	1375	781	318	223	216	261
<b>γ-GTP (IU/L)</b>	--	--	42	30	43	74	71	--	--	--	--
<b>Total protein (g/dL)</b>	--	6.4	6.0	4.0	4.2	4.6	4.7	5.7	4.8	4.9	4.7
<b>BUN (mg/dL)</b>		26.5	51.4	46.3	49.0	25.9	43.4	78.2	58.5	50.8	35.3

<b>Cr (mg/dL)</b>	1.51	2.8	4.93	5.46	4.84	2.58	2.77	3.04	2.65	3.13	1.72
<b>Na (mEq/L)</b>	--	133	137	143	145	136	140	--	--	--	--
<b>K (mEq/L)</b>	--	5.9	5.3	5.1	5.5	4.6	4.6	--	--	--	--
<b>Urine myoglobin (ng/mL)</b>	--	--	840	--	--	--	--	--	--	--	--
<b>CK (CPK) (IU/L)</b>	--	126480	77350	29580	40500	13057	5235	57	55	27	31
<b>CRP (mg/dL)</b>	--	15.0	20.8	11.4	10.8	29.8	24.6	19.7	17.7	17.4	14.1

WBC: White Blood Cell

RBC: Red Blood Cell

PLT: Platelet

AST: Aspartate Aminotransferase

ALT: Alanine Aminotransferase

Al-P: Alkaline Phosphatase

LDH: Lactate Dehydrogenase

$\gamma$ -GTP:  $\gamma$ -Glutamyltranspeptidase

BUN: Blood Urea Nitrogen

Cr: Creatinine

Na: Sodium

K: Potassium

CK (CPK): Creatine Kinase

CRP: C-Reactive Protein

### 3 Leuprorelin Acetate

<b>Brand Name (name of company)</b>	Leuplin for Injection 1.88 and 3.75, Leuplin for Injection Kit 1.88 and 3.75, Leuplin SR for Injection Kit 11.25 (Takeda Pharmaceutical Company Limited)
<b>Therapeutic Category</b>	Hormones-Miscellaneous
<b>Indications</b>	<p>(Leuplin for Injection 1.88)</p> <ul style="list-style-type: none"> <li><input type="radio"/> Endometriosis</li> <li><input type="radio"/> Decrease of myoma volume and/or amelioration of symptoms in uterine myoma with hypermenorrhea, hypogastralgia, low back pain, anemia, etc.</li> <li><input type="radio"/> Central precocious puberty</li> </ul> <p>(Leuplin for Injection 3.75)</p> <ul style="list-style-type: none"> <li><input type="radio"/> Endometriosis</li> <li><input type="radio"/> Decrease of myoma volume and/or amelioration of symptoms in uterine myoma with hypermenorrhea, hypogastralgia, low back pain, anemia, etc.</li> <li><input type="radio"/> Premenopausal breast cancer</li> <li><input type="radio"/> Prostate cancer</li> <li><input type="radio"/> Central precocious puberty</li> </ul> <p>(Leuplin for Injection Kit 1.88)</p> <ul style="list-style-type: none"> <li><input type="radio"/> Endometriosis</li> <li><input type="radio"/> Decrease of myoma volume and/or amelioration of symptoms in uterine myoma with hypermenorrhea, hypogastralgia, low back pain, anemia, etc.</li> </ul> <p>(Leuplin for Injection Kit 3.75)</p> <ul style="list-style-type: none"> <li><input type="radio"/> Endometriosis</li> <li><input type="radio"/> Decrease of myoma volume and/or amelioration of symptoms in uterine myoma with hypermenorrhea, hypogastralgia, low back pain, anemia, etc.</li> <li><input type="radio"/> Premenopausal breast cancer</li> <li><input type="radio"/> Prostate cancer</li> </ul> <p>(Leuplin SR for Injection Kit 11.25)</p> <ul style="list-style-type: none"> <li><input type="radio"/> Prostate cancer</li> </ul>

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

##### [Adverse Reactions (clinically significant adverse reactions)]

Pituitary apoplexy has been reported in patients with pituitary adenoma. Therefore, if headache, vision impairment, visual field disorder, etc. are observed immediately after the first dose of this drug, appropriate measures, such as surgical treatment, should be taken after conducting examination.

##### <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 70s	Prostate cancer (pituitary adenoma)	3.75 mg once	<p><b>Pituitary apoplexy</b></p> <p>2 years before administration: When MRI was performed for the complete medical examination of the cause of headache, tumor (25 × 35 × 20 mm) was confirmed from the intrasellar to suprasellar region. No abnormalities were found in endocrine test. The patient was diagnosed with nonfunctioning pituitary adenoma, and was under follow-up at his own request.</p> <p>On day 1 of administration: As the patient was diagnosed with prostate cancer, this drug was administered. However, 30 minutes after the administration, headache, queasy, oculomotor nerve paralysis of the left eye, and abducent nerve paralysis was developed. The patient was hospitalized in the department of neurosurgery. Consciousness was lucid at time of hospitalization. There was no hypopituitarism or diabetes insipidus. Moreover, CT scan did not confirm clear intratumoral haemorrhage and elective operation was called for. Blood cortisol level was normal and free T<sub>3</sub> and T<sub>4</sub> were slightly decreased. Test results at the time of hospitalization: cortisol 17 µg/dL, free T<sub>3</sub> 1.8 pg/mL, free T<sub>4</sub> 0.8 ng/dL.</p> <p>1 day after administration: MRI findings suggested necrosis at the upper area of the tumor.</p> <p>2 days after administration: Substitution therapy was started to treat pituitary insufficiency.</p> <p>3 days after administration: Blood pressure decreased and blood cortisol decreased (3.1 µg/dL) were confirmed.</p> <p>9 days after administration: MRI findings suggested progression of necrosis within the tumor, as well as intratumoral haemorrhage.</p> <p>13 days after administration: Haematoma and tumor were removed through transsphenoidal sinus operation.</p> <p>10 months after administration: Left abducent nerve paralysis slightly remained, and pituitary insufficiency was confirmed.</p>	Company report
Concomitant medications: unknown					

## 4 Lopinavir/Ritonavir

<b>Brand Name (name of company)</b>	Kaletra Soft Capsules, Kaletra Liquid (Abbott Japan Co., Ltd.)
<b>Therapeutic Category</b>	Antivirals
<b>Indications</b>	HIV infection

<<PRECAUTIONS (underlined parts are additions)>>

[Contraindications]

Patients receiving the following drugs: pimoziide, cisapride, ergotamine tartrate, dihydroergotamine mesilate, midazolam, triazolam, varденафил hydrochloride hydrate

[Important Precautions]

Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If any such abnormality is noted, appropriate measures should be instituted.  
Immune reconstructive 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.

[Interactions (contraindications for concomitant use)]

Vardenafil hydrochloride hydrate

[Adverse Reactions (clinically significant adverse reactions)]

**Bradycardia:** Bradycardia (sinus bradycardia, sinus arrest, atrioventricular block) may occur.  
**Erythema multiforme, oculomucocutaneous syndrome (Stevens-Johnson syndrome):** Erythema multiforme and oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur.

<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 20s	HIV infection (haemophilia A, hepatitis B, hepatitis C)	6 capsules 2 days ↓ (no administration for 50 days) ↓ 6 capsules 4 days	<p><b>Atrioventricular block complete, atrioventricular block second degree (Wenckebach type)</b></p> <p>28 days before administration: Anti-HIV therapy was started from 7 years ago. The patient was hospitalized to undergo salvage therapy for end stage AIDS.</p> <p>On day 1 of administration: Administration of this drug and didanosine was initiated.</p> <p>On day 2 of administration (day of discontinuation): Queasy and palpitations occurred. Administration of this drug and didanosine was discontinued. Atrioventricular block complete was found by electrocardiogram. The symptoms were improved through intravenous injection of atropine sulfate. Heart rate was controlled through oral administration of orciprenaline sulfate. Thereafter, complete atrioventricular block was confirmed 1 day and also 14 days after discontinuation.</p> <p>2 days after discontinuation: Atrioventricular block second degree (Wenckebach type) was confirmed during the night. Thereafter, atrioventricular block second degree was confirmed by holter electrocardiogram on 3, 19, 21, 31, and 35 days after discontinuation.</p>	Company report

				<p>15 days after discontinuation: The patient was recovered from atrioventricular block complete.</p> <p>46 days after discontinuation: There was no recurrence of atrioventricular block complete since the final occurrence on 14 days after discontinuation. The patient was discharged from the hospital.</p> <p>51 days after discontinuation (On day 1 of readministration): The patient was rehospitalized for readministration of this drug and didanosine. Administration of this drug and didanosine was started on the same day.</p> <p>On day 2 of readministration: The patient complained of chest discomfort in the early morning. Atrioventricular block second degree (Wenckebach type) was confirmed by electrocardiogram. Thereafter, there were sporadic occurrences of atrioventricular block second degree (Wenckebach type) on day 3 and 4 of readministration.</p> <p>Chest discomfort improved through a 5% load of glucose lactated Ringer's solution and atropine sulfate at 0.5 mg.</p> <p>On day 4 of readministration (day of discontinuation): Administration of this drug and didanosine was discontinued in accordance with the patient's wishes.</p> <p>Chest discomfort was felt even after discontinuation of administration.</p> <p>1 day after discontinuation: Thereafter, atrioventricular block second degree (Wenckebach type) was not observed. The patient was recovered from atrioventricular block second degree (Wenckebach type).</p> <p>3 days after discontinuation: Chest discomfort resolved. Oral administration of orciprenaline sulfate was continued and the patient was discharged from the hospital.</p> <p>4 days after discontinuation: Administration of sanilvudine, lamivudine, and nelfinavir was started. 17 days after discontinuation, administrations of these drugs were discontinued. Thereafter, atrioventricular block second degree (Wenckebach type) was confirmed on 27 days after discontinuation and atrioventricular block was confirmed on 31 days after discontinuation. Thereafter, arrhythmia events including atrioventricular block second degree (MobitzII type) were observed until the 35 days after discontinuation.</p> <p>35 days after discontinuation: The patient was recovered from atrioventricular block.</p>	
<p>Concomitant medications: didanosine (suspected drug), interferon alfa-2b (Genetical recombination), freeze-dried human blood coagulation factor VIII concentrate, sulfamethoxazole/trimethoprim, ribavirin</p>					

## Revision of PRECAUTIONS (No. 166)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 213) (excluding those presented in “1. Important Safety Information” of this Bulletin), together with reference materials.

### 1 <Antiparkinsonian agents> Cabergoline

<b>[Brand Name]</b>	Cabaser Tab. 0.25 mg and 1.0 mg (Pfizer Japan Inc.)
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<p><b>Pleural effusion, changes such as pleural fibrosis, or pulmonary fibrosis, pericarditis:</b> Pleural effusion may occur. Furthermore, if this drug is administered in a patient previously treated with this drug over the long term or an ergot preparation possessing dopamine receptor stimulating action, pleural fibrosis, pulmonary fibrosis, or pericarditis may occur. If oedema or respiratory symptoms etc. occur during the administration, chest X-ray examination should be immediately conducted. If abnormalities are observed, discontinue administration and take appropriate measures.</p> <p><b>Cardiac valvulopathy:</b> <u>If there is onset or aggravation of cardiac murmurs, chest X-ray or echocardiography tests etc. should be immediately conducted and if valve abnormalities are observed, discontinue administration and take appropriate measures.</u></p>
<b>&lt;Reference Information&gt;</b>	Company report

### 2 <Antiarrhythmic agents> Nifekalant Hydrochloride

<b>[Brand Name]</b>	Shinbit Injection (Nihon Schering K.K.)
<b>[Precautions of Dosage and Administration]</b>	<u>As this drug may induce compatibility through its concomitant use with another drug or due to preparation conditions, extra caution should be exercised in selecting drugs and preparation conditions, etc.</u>
<b>&lt;Reference Information&gt;</b>	Company report

### 3 <Hyperlipidaemia agents> Pitavastatin Calcium

<b>[Brand Name]</b>	Livalo Tablets 1 mg and 2 mg (Kowa Company, Ltd.)
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<b>Platelets decreased:</b> <u>Platelets decreased may occur. Patients should be carefully monitored through blood tests etc. If abnormalities are observed, discontinue administration and take appropriate measures.</u>
<b>&lt;Reference Information&gt;</b>	Company report

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<Cardiovascular agents-Miscellaneous>

#### 4 Limaprost Alfadex

**[Brand Name]** Opalmon Tablets (Ono Pharmaceutical Co., Ltd.), Prorenal Tablets (Dainippon Pharmaceutical Co., Ltd.), and others

**[Adverse Reactions (clinically significant adverse reactions)]** Hepatic function disorder or jaundice: Hepatic function disorder or jaundice with significant elevations of AST (GOT)·ALT (GPT) may occur. Patients should be carefully monitored. If abnormalities are observed, appropriate therapeutic measures such as discontinuing the administration should be taken.

**<Reference Information>** Company report

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<Antitussives, Antitussives and expectorants>

#### 5 Dextromethorphan Hydrobromide, Dextromethorphan Hydrobromide/Potassium Cresolsulphonate

**[Brand Name]** Medicon Powder, Medicon Tablets 15 mg, Medicon Syrup (Shionogi & Co., Ltd.), and others

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

**<Reference Information>** Company report

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<Urogenital and anal organ agents-Miscellaneous>

#### 6 Vardenafil Hydrochloride Hydrate

**[Brand Name]** Levitra Tablets 5 mg and 10 mg (Bayer Yakuhin, Ltd.)

**[Contraindications]** Patients under treatment with ritonavir, indinavir, atazanavir, saquinavir, saquinavir mesilate, fosamprenavir, lopinavir/ritonavir  
Patients under treatment with ketoconazole or itraconazole

**[Interactions (contraindications for concomitant use)]** Atazanavir, saquinavir, saquinavir mesilate, fosamprenavir, lopinavir/ritonavir

**<Reference Information>** Company report

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<Miscellaneous metabolism agents>

#### 7 Zoledronic Acid Hydrate

**[Brand Name]** Zometa Injection 4 mg (Novartis Pharma K.K.)

**[Important Precautions]** Osteonecrosis of the jaw and osteomyelitis may occur in cancer patients with a medical history of dental procedures such as tooth extraction etc. and who are concurrently receiving chemotherapy or corticosteroid therapy. If this drug is administered to patients with risk factors (malignant tumor, chemotherapy, corticosteroid therapy, poor oral hygiene, a medical history of dental procedures etc.), patients should be first received an appropriate dental examination. Patients should avoid invasive dental procedures as much as possible during treatment with this drug.

**<Reference Information>** Company report

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<Allergic agents-Miscellaneous>

## 8 Ramatroban

[Brand Name] Baynas Tablets 50 mg and 75 mg (Bayer Yakuhin, Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatitis, hepatic function disorder, jaundice:** Hepatitis, hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), Al-P,  $\gamma$ -GTP, and LDH levels, etc. and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

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<Synthetic antibacterials>

## 9 Tosufloxacin Tosilate

[Brand Name] Ozex Tablets 75 and 150 (Toyama Chemical Co., Ltd.), Tosuxacin Tablets 75 mg and 150 mg (Abbott Japan Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] Serious nephropathy such as acute renal failure or interstitial nephritis may develop. The patients should be carefully monitored through periodic renal function test etc. If abnormality is observed, administration should be discontinued and appropriate measures should be taken.

Hypoglycemia may develop (especially for elderly patients, patients with renal dysfunction, and patients with diabetes mellitus). The patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

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<Antivirals>

## 10 Atazanavir Sulfate

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

[Important Precautions] Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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

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<Antivirals>

## 11 Abacavir Sulfate, Amprenavir, Indinavir Sulfate Ethanolate, Efavirenz, Sanilvudine, Zalcitabine, Didanosine, Zidovudine, Delavirdine Mesilate, Nevirapine, Nelfinavir Mesilate, Ritonavir

[Brand Name] Ziagen Tablets (GlaxoSmithKline K.K.), Prozei Capsules (Kissei Pharmaceutical Co., Ltd.), Crixivan Capsules (Banyu Pharmaceutical Co., Ltd.), Stocrin Capsules 200 (Banyu Pharmaceutical Co., Ltd.), Zerit Capsules 15 and 20 (Bristol Myers K.K), Hivid Tablets 0.375 (Chugai Pharmaceutical Co., Ltd.), Videx Chewable/Dispersible Buffered Tablets 25, 50, and 100, Videx EC Capsules Enteric-Coated Beadlets 125 and 200 (Bristol Myers K.K), Retrovir Capsules (GlaxoSmithKline K.K.), Rescriptor Tablets 200 mg (Pfizer Japan Inc.), Viramune Tablets 200 (Nippon Boehringer Ingelheim Co., Ltd.), Viracept Tab. (Japan Tobacco Inc.), Norvir-Soft Capsules 100 mg, Norvir-Liquid (Abbott Japan Co., Ltd.)

[Important Precautions] Body fat redistribution/accumulation may occur following the use of anti-HIV

drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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

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12 <Antivirals>  
**Saquinavir, Saquinavir Mesilate**

[Brand Name] Fortovase Caps., Invirase Capsules (Chugai Pharmaceutical Co., Ltd.)

[Contraindications] Patients under treatment with terfenadine, astemizole, cisapride, pimozone, amiodarone, bepridil, ergotamine preparation, or vardenafil

[Important Precautions] Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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.

[Interactions (contraindications for concomitant use)] Vardenafil

<Reference Information> Company report

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13 <Antivirals>  
**Zidovudine/Lamivudine**

[Brand Name] Combivir Tablets (GlaxoSmithKline K.K.)

[Warning] **WARNING**  
Recurrent chronic hepatitis B may occur in patients with concomitant chronic hepatitis B on discontinuation of lamivudine. Extra caution should be exercised when discontinuing administration of this drug, especially for when dealing with decompensated patients as the disease may become serious.

[Important Precautions] “Recurrent chronic hepatitis B may occur in patients with concomitant chronic hepatitis B on discontinuation of lamivudine. Extra caution should be exercised when discontinuing administration of this drug.” was omitted.  
Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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

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14 <Antivirals>  
**Fosamprenavir Calcium Hydrate**

[Brand Name] Lexiva Tablets 700 (GlaxoSmithKline K.K.)

[Contraindications] Patients under treatment with vardenafil hydrochloride hydrate

[Important Precautions] Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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.

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

<Reference Information> Company report

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15 <Antivirals>  
**Lamivudine (150 mg, 300 mg)**

[Brand Name] Epivir Tablets 150 and 300 (GlaxoSmithKline K.K.)

[Warning] **WARNING**  
Recurrent chronic hepatitis B may occur in patients with concomitant chronic hepatitis B on discontinuation of this drug. Extra caution should be exercised when discontinuing administration of this drug, especially for when dealing with decompensated patients as the disease may become serious.

[Important Precautions] “Recurrent chronic hepatitis B may occur in patients with concomitant chronic hepatitis B on discontinuation of this drug. Extra caution should be exercised when discontinuing administration of this drug.” was omitted.  
Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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

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16 <Antivirals>  
**Lamivudine/Abacavir Sulfate**

[Brand Name] Epzicom Tablets (GlaxoSmithKline K.K.)

[Warning] **WARNING**  
Recurrent chronic hepatitis B may occur in patients with concomitant chronic hepatitis B on discontinuation of lamivudine. Extra caution should be exercised when discontinuing administration of this drug, especially for when dealing with decompensated patients as the disease may become serious.

**[Important Precautions]**

“Recurrent chronic hepatitis B may occur in patients with concomitant chronic hepatitis B on discontinuation of lamivudine. Extra caution should be exercised when discontinuing administration of this drug, especially for when dealing with decompensated patients as the disease may become serious.” was omitted.

Body fat redistribution/accumulation may occur following the use of anti-HIV drugs. If abnormalities are observed, appropriate measures should be taken. Immune reconstructive 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

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### 3

## List of products subject to Early Post-marketing Phase Vigilance

(As of June 1, 2005)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
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* <sup>1</sup>	GlaxoSmithKline K.K.	December 8, 2004
Ribavirin ----- Rebetol Capsules 200 mg* <sup>2</sup>	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
Beclometasone Dipropionate ----- Qvar Aerosol 50 and 100* <sup>3</sup>	Dainippon Pharmaceutical Co., Ltd.	January 19, 2005
Zoledronic Acid Hydrate ----- Zometa Injection 4 mg	Nihon Ciba-Geigy K.K.	January 21, 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* <sup>4</sup>	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
Rosuvastatin Calcium ----- Crestor Tablets 2.5 mg and 5 mg	AstraZeneca K.K.	April 27, 2005

Note) Subject to additional indication etc.

- \*1: An additional indication for “in case of concurrent use with adefovir pivoxil”
- \*2: An additional indication for “improvement of viraemia in the following chronic hepatitis C cases through concomitant use with peginterferon alfa-2b (Genetical recombination)”
- \*3: 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)”
- \*4: An additional indication for “Rheumatoid arthritis (only for cases which are not adequately responsive to conventional therapies”