Pharmaceuticals and Medical Devices Safety Information

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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

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

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

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Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated October 27, 2006, together with reference information.

1 Tacrolimus Hydrate (capsules 0.5 mg, 1 mg)

Brand Name (name of company)	Prograf Capsules 0.5 mg and 1 mg (Astellas Pharma Inc.)
Therapeutic Category	Miscellaneous metabolism agents
Indications	1. Suppression of organ rejection in the following organ transplantation Kidney transplantation, liver transplantation, heart transplantation, lung transplantation, pancreas transplantation 2. Suppression of graft rejection and GVHD in bone marrow transplantation 3. Systemic myasthenia gravis (in a case where the effect of steroids is insufficient or the administration is difficult because of adverse reactions in the treatment after thymectomy) 4. Rheumatoid arthritis which is not adequately responsive to conventional therapies

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

[Careful Administration]	Patients with rheumatoid arthritis coexisting interstitial pneumonia
[Adverse Reactions (clinically significant adverse reactions)]	**Aggravation of interstitial pneumonia:** In patients with rheumatoid arthritis coexisting interstitial pneumonia, interstitial pneumonia may be aggravated. Therefore, patients should be carefully observed, and if respiratory symptoms such as pyrexia, cough, or dyspnoea develop, the drug should be discontinued. Affected patients should be promptly examined by chest X-ray and CT scan, as well as blood testing, and appropriate measures, including administration of adrenocortical hormone, should be implemented. Differential diagnosis of infection should be taken into consideration. **Diabetes mellitus, hyperglycaemia:** Since diabetes mellitus may occur newly or may be aggravated, or hyperglycaemia may occur, patients should be carefully observed. If any abnormalities are observed, appropriate measures such as dose reduction or drug cessation should be taken.
<Reference Information>	The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to September 22, 2006) (events for which a causality to the drug could not be denied) • Aggravation of interstitial pneumonia: 10 cases (of which 2 had a fatal case) • Diabetes mellitus and hyperglycaemia: 13 cases (no fatal case) The number of patients treated with Tacrolimus for a year estimated by MAH (Marketing Authorisation Holder): approximately 15000 (of which approximately 5000 used it for rheumatoid arthritis) (October 2005 to September 2006) Marketed in Japan in: June 1993 (date of approval of an additional indication for rheumatoid arthritis: April 2005)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 60s	Malignant rheumatoid arthritis (interstitial pneumonia, Sjogren's Syndrome, hypertension)	1 mg 14 days ↓ 1.4 mg 107 days	**Aggravation of interstitial pneumonia** Approx. 5 years before administration: The patient developed malignant rheumatoid arthritis. Approx. 4 years before administration: Salazosulfapyridine at 1g was started for malignant rheumatoid arthritis. 14 days before administration: WBC 5700/mm^3, RBC sedimentation rate 118 mm/hr, CRP 5.3 mg/dL, KL-6 892 U/mL On day 1 of administration: Tacrolimus at 1 mg was started for the treatment of malignant rheumatoid arthritis. The patient had concurrent interstitial pneumonia from the beginning. On day 15 of administration: Salazosulfapyridine was discontinued and the dose of tacrolimus was increased to 1.4 mg. On day 36 of administration: Blood concentration of this drug, WBC, RBC sedimentation rate, CRP, and KL-6 were 4.4 ng/mL, 6300/mm^3, 98 mm/hr, 1.9 mg/dL, and 929 U/mL, respectively. Approx. in month 2 of administration: Cough/respiratory discomfort developed. On day 71 of administration: Blood concentration of this drug, WBC, RBC sedimentation rate, CRP, and KL-6 were 6.2 ng/mL, 5800/mm^3, 64 mm/hr, 0.9 mg/dL, and 1051 U/mL, respectively. On day 106 of administration: Blood concentration of this drug, WBC, RBC sedimentation rate, CRP, and KL-6 were 4.7 ng/mL, 10200/mm^3, 105 mm/hr, 1.3 mg/dL, and 5321 U/mL, respectively. On day 116 of administration: Aggravation of interstitial pneumonia was diagnosed by chest X-ray on outpatient visit. WBC, LDH, CRP, and KL-6 were 10700/mm^3, 360 IU/L, 2.5 mg/dL, 5292 U/mL, respectively. On day 120 of administration: Patient was admitted to hospital due to acute aggravation. Oxygen cannula was 2 L/min. Blood concentration of this product, WBC, LDH, CRP, β-D-glucan, KL-6, and cytomegalovirus IgM were 3.9 ng/mL, 8900/mm^3, 384 IU/L, 2.3 mg/dL, ≤5.0 pg/mL, 4489 U/mL, and (−), respectively. On day 121 of administration (day of discontinuation): Tacrolimus was discontinued. 1 day after discontinuation: Oxygen cannula was 3 L/min. DLST for tacrolimus was negative. 2 days after discontinuation: WBC, LDH, CRP, KL-6, mycoplasma IgM were 6100/mm^3, 330 IU/L, 4.4 mg/dL, 4273 U/mL, and (−), respectively.	Company report

				10 days after discontinuation: Prednisolone at 70 mg was started. 97 days after discontinuation: Outcome was improved. The patient was discharged from hospital. Home oxygen therapy (HOT) was started (3 L/min). Subsequently, the dose of prednisolone was reduced to 30 mg. The symptoms were stable.	
	Concomitant medications: salazosulfapyridine, amlodipine besilate				

Clinical Laboratory Values

	14 days before administration	On day 36 of administration	On day 71 of administration	On day 106 of administration	On day 116 of administration	On day 120 of administration	2 days after discontinuation
WBC (/mm^3)	5700	6300	5800	10200	10700	8900	6100
CRP (mg/dL)	5.3	1.9	0.9	1.3	2.5	2.3	4.4
LDH (IU/L)	--	--	--	--	360	384	330
RBC sedimentation rate (mm/hr)	118	98	64	105	--	--	--
β-D-glucan (pg/mL)	--	--	--	--	--	≤5.0	--
KL-6 (U/mL)	892	929	1051	5321	5292	4489	4273
Blood tacrolimus concentration (ng/mL)	--	4.4	6.2	4.7	--	3.9	--

WBC: White Blood Cell CRP: C-Reactive Protein
LDH: Lactate Dehydrogenase RBC: Red Blood Cell

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Rheumatoid arthritis (interstitial pneumonia, hyperlipidemia, gastric ulcer)	2 mg 14 days ↓ 3 mg 100 days	**Acute aggravation of interstitial pneumonia** Approx. 1 and a half year before administration: The patient developed rheumatoid arthritis. Interstitial pneumonia occurred concomitantly. 71 days before administration: KL-6 390 U/mL 7 days before administration: LDH, WBC, erythrocyte sedimentation rate, CRP, BUN, and K were 283 IU/L, 18200/mm^3, 39 mm/hr, 0.92 mg/dL, 20.9 mg/dL, and 3.3 mEq/L, respectively. On day 1 of administration: Tacrolimus at 2 mg was started for the treatment of rheumatoid arthritis. At the time of starting tacrolimus, the rheumatoid arthritis was classified as Steinbrocker Stage II and Class 1. LDH, WBC, erythrocyte sedimentation rate, CRP, BUN, K were 280 IU/L, 17900/mm^3, 48 mm/hr, 0.76 mg/dL, 17.4 mg/dL, 3.3 mEq/L, respectively. Administration of the drugs that had been administered for the treatment of rheumatoid arthritis before starting tacrolimus (prednisolone 12 mg, meloxicam 10 mg, and loxoprofen sodium 120 mg) was continued. On day 15 of administration: The dose of tacrolimus was increased to 3 mg. On day 107 of administration: Around this day, the patient began to notice dyspnoea with activity.	Company report

				On day 110 of administration: Pyrexia of 37.8°C occured. The patient experienced dyspnoea also at rest. On day 111 of administration: The patient made outpatient visit. He had severe dyspnoea at the beginning of his vist. SpO_2 was decreased to 80%. Ground-glass opacity was observed on both sides by chest X-ray and CT and acute aggravation of interstitial pneumonia was diagnosed. The patient was admitted to hospital. Steroid pulse therapy was started with methylprednisolone sodium succinate at 1.0 g. Pneumocystis jiroveci pneumonia was also suspected (elevation of β-D-glucan was observed). Oral administration of sulfamethoxazole/trimethoprim at 12 g was started. In addition, 1.0g of sulbactam sodium/cefoperazone sodium was started since bacterial infectious disorders could not be denied due to the high WBC on admission ($20100/mm^3$). SpO_2 was 85% to 95% while on oxygen (≥15 L/min). Prednisolone, meloxicam, and loxoprofen sodium were discontinued. LDH, erythrocyte sedimentation rate, CRP, BUN, K, β-D-glucan, KL-6, SP-D were 488 IU/L, 53 mm/hr, 17.33 mg/dL, 22.7 mg/dL, 3.9 mEq/L, ≥272.6 pg/mL, 931 U/mL, 116 ng/mL, respectively. Infusion of ganciclovir was started, but interrupted after three days of treatment because (CMV) antigen was negative on admission. On day 112 of administration: Oral administration of sulfamethoxazole/trimethoprim became difficult for the patient, and was discontinued. Infusion of pentamidine isetionate at 240 mg was started. Steroid pulse therapy was completed. On day 114 of administration (day of discontinuation): The patient developed hyperkalaemia. Furosemide was started for the treatment of hyperkalaemia. Prednisolone was restarted at 10 mg. Tacrolimus was discontinued. LDH, WBC, CRP, BUN, and K were 451 IU/L, $20700/mm^3$, 6.18 mg/dL, 19.7 mg/dL, 5.5 mEq/L, respectively. 2 days after discontinuation: Sulbactam sodium/cefoperazone sodium was discontinued and meropenem trihydrate at 1.0 g was started. The patient was intubated and connected to a respirator. 3 days after discontinuation: BUN increased. LDH, WBC, CRP, BUN, K, and β-D-glucan were 497 IU/L, $25100/mm^3$, 30.68 mg/dL, 37.3 mg/dL, 6.1 mEq/L, 159.2 pg/mL, respectively.	

				4 days after discontinuation: Steroid pulse therapy with methylprednisolone sodium succinate at 1.0 g was performed (the 2nd course). LDH, WBC, CRP, BUN, and K were 503 IU/L, 24400/mm^3, 27.07 mg/dL, 34.6 mg/dL, and 6.1 mEq/L, respectively. 5 days after discontinuation: SpO_2 was between 95% and 97%. The observation was continued. 6 days after discontinuation: The steroid pulse therapy was completed. LDH, WBC, erythrocyte sedimentation rate, β-D-glucan, BUN, CMV antigen, and K were 341 IU/L, 19100/mm^3, 101 mm/hr, 106.1 pg/mL, 42.1 mg/dL, (+), and 6.1 mEq/L, respectively. 7 days after discontinuation: CMV pneumonia could not be denied. Infusion of ganciclovir was restarted at 500 mg. 8 days after discontinuation: Steroid pulse therapy with methylprednisolone sodium succinate at 1.0 g was performed (the 3rd course). 10 days after discontinuation: The steroid pulse therapy was completed. LDH, WBC, erythrocyte sedimentation rate, BUN, K, KL-6, and SP-D were 496 IU/L, 35200/mm^3, 16 mm/hr, 61.3 mg/dL, 5.4 mEq/L, 1500 U/mL, and 431 ng/mL, respectively. 11 days after discontinuation: Steroid pulse therapy with methylprednisolone sodium succinate at 1.0 g was performed (the 4th course), and completed on the day. LDH, WBC, CRP, β-D-glucan, BUN, and K were 600 IU/L, 31700/mm^3, 6.36 mg/dL, 164.4 pg/mL, 73.6 mg/dL, 5.0 mEq/L. 12 days after discontinuation: In the morning, the patient died of respiratory failure due to interstitial pneumonia. Pneumocystis jiroveci pneumonia, hyperkalaemia, and BUN increased were not resolved. Administration of ganciclovir, meropenem trihydrate, and pentamidine isetionate were continued until this day. The patient's pneumocystis jiroveci pneumonia, which was suspected from the high β-D-glucan level on admission, could not be proven by identifying the fungus in sputum (since no sputum sample could be collected).	
	Concomitant medications: prednisolone, meloxicam, loxoprofen sodium, atorvastatin calcium, omeprazole, polaprezinc, rebamipide, alendronate sodium hydrate				

Clinical Laboratory Values

	71 days before administration	7 days before administration	On day 1 of administration	On day 111 of administration	On day 114 of administration (day of discontinuation)	3 days after discontinuation	4 days after discontinuation	6 days after discontinuation	10 days after discontinuation	11 days after discontinuation
WBC (/mm^3)	--	18200	17900	20100	20700	25100	24400	19100	35200	31700
Lymphocyte count (/mm^3)	--	--	--	3300	800	--	400	700	300	--
CRP (mg/dL)	--	0.92	0.76	17.33	6.18	30.68	27.07	--	--	6.36
LDH (IU/L)	--	283	280	488	451	497	503	341	496	600
BUN (mg/dL)	--	20.9	17.4	22.7	19.7	37.3	34.6	42.1	61.3	73.6
Erythrocyte sedimentation rate (mm/hr)	--	39	48	53	--	--	--	101	16	--
K (mEq/L)	3.7	3.3	3.3	3.9	5.5	6.1	6.1	6.1	5.4	5.0
β-D-glucan (pg/mL)	--	--	--	≥272.6	--	159.2	--	106.1	--	164.4
KL-6 (U/mL)	390	--	--	931	--	--	--	--	1500	--
SP-D (ng/mL)	--	--	--	116	--	--	--	--	431	--
CMV antigen	--	--	--	(–)	--	--	--	(+)	--	--

WBC: White Blood Cell
CRP: C-Reactive Protein
LDH: Lactate Dehydrogenase
SP-D: Pulmonary Surfactant Protein-D
CMV: Cytomegalovirus

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 40s	Liver transplant (hepatitis C virus)	2 to 3 mg approx. 10 months	**Diabetes mellitus** Approx. 2 years before administration: Type C hepatic cirrhosis was diagnosed. Before administration: HbA_{1c} 3.7% The patient received a liver transplant from his wife as a living donor for type C hepatic cirrhosis. On day 1 of administration: Tacrolimus (2-3mg) for post-transplantation immunosuppression and ribavirin and peginterferon alfa-2b (Genetical recombination) for hepatitis C virus infectious disorder were started. Ursodeoxycholic acid, cilostazol, mecobalamin, and sodium rabeprazole were also started around this day. In month 1 of administration: Peginterferon alfa-2b (Genetical recombination) was discontinued. Peginterferon alfa-2a (Genetical recombination) at 90 μg/week was started. In month 3 of administration: HbA_{1c} 4.6% In month 5 of administration: Sugar in urine (−), urine ketone (−), blood tacrolimus concentration 12.7 ng/mL. In month 6 of administration: Sugar in urine (−), urine ketone (−), blood tacrolimus concentration 9.5 ng/mL In month 6.5 of administration: The patient started testing positive for sugar in urine around this day. Sugar in urine was (+). In month 7 of administration: Sugar in urine 30 mg/dL, sugar in urine (±), urine ketone (−), blood tacrolimus concentration 5.2 ng/mL In month 7.5 of administration: Sugar in urine (−), urine ketone (−), blood tacrolimus concentration 6.1 ng/mL In month 8 of administration: Peginterferon alfa-2a (Genetical recombination) was discontinued. Sugar in urine 300 mg/dL, sugar in urine (3+), urine ketone (+), blood tacrolimus concentration 11.5 ng/mL peginterferon alfa-2b (Genetical recombination) at 50 μg/week was started. In month 8.5 of administration: Sugar in urine (4+), urine ketone (−), fasting blood glucose (FBG) 319 mg/dL, HbA_{1c} 5.8%. The patient was referred to our department. The chief complaints were thirst and polydipsia/polyuria. Blood tacrolimus concentration was 3.9 mg/mL. The patient was followed up at our department hereafter.	Company report

				In month 9 of administration: Sugar in urine 500 mg/dL, sugar in urine (3+), urine ketone (−), FBG 246 mg/dL, HbA_{1c} 5.9%, blood tacrolimus concentration 3.6 ng/mL. In month 9.5 of administration: Sugar in urine (4+), urine ketone 10 mg/dL, urine ketone (+), FBG 361 mg/dL, HbA_{1c} 6.7%, blood tacrolimus concentration <3.5 ng/mL. In month 10 of administration: The patient was admitted. FBG on admission 389 mg/dL, sugar in urine (4+), urine ketone (+). FBG 284 mg/dL, HbA_{1c} 7.5%, blood tacrolimus concentration 5.0 ng/mL, glycoalbumin 42.1%, insulin 3.6 μU/mL. Insulin therapy was started. (day of discontinuation): FBG was 220 mg/dL after insulin treatment at 50 U/day. Good blood glucose control was not achieved. Tacrolimus was discontinued. 1 day after discontinuation: FBG was 212 mg/dL. 3 days after discontinuation: FBG was 220 mg/dL. 5 days after discontinuation: FBG was 204 mg/dL. FBG was changed in the range of 100 to 150 mg/mL level hereafter. 13 days after discontinuation: 7 blood glucose measurements by the patient were 135 mg/dL (before breakfast), 138 mg/dL (after breakfast), 118 mg/dL (before lunch), 146 mg/dL (after lunch), 123 mg/dL (before dinner), 120 mg/dL (after dinner), and 181 mg/dL (before sleep). Insulin dose was 10 U/day. 16 days after discontinuation: FBG was 125 mg/dL. Good blood glucose control was achieved. The interferon therapy was continued. 27 days after discontinuation: The patient was discharged.	
	Concomitant medications: peginterferon alfa-2a (Genetical recombination), peginterferon alfa-2b (Genetical recombination), mycophenolate mofetil, ribavirin, sodium rabeprazole, magnesium oxide, ursodeoxycholic acid, cilostazol, mecobalamin				

Clinical Laboratory Values

	Before administration	In month 3 of administration	In month 5 of administration	In month 6 of administration	In month 6.5 of administration	In month 7 of administration	In month 7.5 of administration	In month 8 of administration	In month 8.5 of administration
FBG (mg/dL)	--	--	--	--	--	--	--	--	319
RBG (mg/dL)	--	--	--	--	--	--	--	--	--
HbA_{1c} (%)	3.7	4.6	--	--	--	--	--	--	5.8
Sugar in urine	--	--	(−)	(−)	(+)	(±) 30 mg/dL	(−)	(3+) 300 mg/dL	(4+)
Urine ketone	--	--	(−)	(−)	--	(−)	(−)	(+)	(−)
Glycoalbumin (%)	--	--	--	--	--	--	--	--	--
Insulin (μU/mL)	--	--	--	--	--	--	--	--	--
Blood tacrolimus concentration (ng/mL)	--	--	12.7	9.5	--	5.2	6.1	11.5	3.9

FBG: Fasting Blood Glucose
RBG: Random Blood Glucose
HbA_{1c}: Haemoglobin A_{1c}

	In month 9 of administration	In month 9.5 of admin.	In month 10 of admin. (4 days before discontinuation)	In month 10 of admin. (3 days before discontinuation)	In month 10 of admin. (day of discontinuation)	1 day after discontinuation	3 days after discontinuation	5 days after discontinuation	16 days after discontinuation
FBG (mg/dL)	246	361	389	284	220	212	220	204	125
RBG (mg/dL)	--	--	--	404	289	304	243	227	--
HbA_{1c} (%)	5.9	6.7	--	7.5	--	--	--	--	--
Sugar in urine	(3+) 500 mg/dL	(4+)	(4+)	--	--	--	--	--	--
Urine ketone	(–)	(+) 10 mg/dL	(+)	--	--	--	--	--	--
Glycoalbumin (%)	--	--	--	42.1	--	--	--	--	--
Insulin (μU/mL)	--	--	--	3.6	--	--	--	--	--
Blood tacrolimus concentration (ng/mL)	3.6	<3.5	--	5.0	--	--	--	--	--

FBG: Fasting Blood Glucose
RBG: Random Blood Glucose
HbA_{1c}: Haemoglobin A_{1c}

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Female 70s	Rheumatoid arthritis (diabetes mellitus, hypertension, diabetic nephropathy, diabetic retinopathy, asthma, gastric ulcer, angina pectoris, anxiety)	1 mg 14 days ↓ 2 mg 29 days	**Hyperglycaemia** Unknown: The patient developed hypertension. Valsartan was started for the treatment of hypertension (The day of treatment initiation was unknown). Approx. 23 years before administration: The patient developed diabetes mellitus. Approx. 10 years before administration: The patient received a diagnosis of rheumatoid arthritis (RA) at the orthopedic department of another hospital. Approx. 6 years before administration: The patient was referred to our hospital. Unknown: The renal function was aggravated by diabetes and RA. Nateglinide 270 mg was started for the treatment of diabetes mellitus (The day of treatment initiation was unknown). Approx. 5 years before administration: The RA was classified as Steinbrocker Stage III and Class 3. Unknown: Famotidine at 40 mg was started for the treatment of gastric ulcer.	Company report

				153 days before administration: K 4.6 mEq/L, BUN 20.7 mg/dL, blood glucose (BG) 131 mg/dL, HbA_{1c} 6.0%, Cr 0.84 mg/dL. 42 days before administration: K 4.9 mEq/L, BUN 26.1 mg/dL, BG 162 mg/dL, Cr 0.90 mg/dL On day 1 of administration: Tacrolimus at 1 mg was started for the treatment of RA. On day 15 of administration: The dose of tacrolimus was increased to 2 mg. On day 29 of administration: BUN and Cr increased. BUN 24.7 mg/dL, Cr 0.92 mg/dL. On day 30 of administration: Aggravation in BG control was noted. Metformin hydrochloride was started. BG 312 mg/dL, HbA_{1c} 6.7% On day 34 of administration: The patient was hospitalized. On day 35 of administration: Nateglinide was discontinued. Insulin lispro (Genetical recombination) was started. BG was 147 mg/dL. On day 36 of administration: Metformin hycdochloride was discontinued. On day 37 of administration: K and BUN increased. Changes were made from amlodipine besilate to benidipine hydrochloride 4 mg and from famotidine to lansoprazole 30 mg. K 5.2 mEq/L, BUN 28.8 mg/dL, Cr 1.09 mg/dL On day 42 of administration: K 5.9 mEq/L, BUN 28.3 mg/dL, BG 197 mg/dL, Cr 0.99 mg/dL On day 43 of administration (day of discontinuation): Tacrolimus, valsartan, and insulin lispro (Genetical recombination) were discontinued. 1 day after discontinuation: Nateglinide was restarted. 5 days after discontinuation: Hyperglycaemia and BUN increased were improved. K was improved, Cr became normal. K 5.2 mEq/L, BUN 26.5 mg/dL, Cr 0.91 mg/dL 8 days after discontinuation: The patient was discharged. Administration of nateglinide was continued.	
	Concomitant medications: ibuprofen, nateglinide, aspirin, famotidine, lansoprazole, valsartan, benidipine hydrochloride, doxazosin mesilate, amlodipine besilate, nicorandil, pranlukast hydrate, tulobuterol, etizolam				

Clinical Laboratory Values

	153 days before administration	42 days before administration	On day 29 of administration	On day 30 of administration	On day 35 of administration	On day 37 of administration	On day 42 of administration	5 days after discontinuation
BG (mg/dL)	131	162	--	312	147	--	197	--
HbA_{1c} (%)	6.0	--	--	6.7	--	--	--	--
Sugar in urine	(–)	--	--	(2+)	(–)	--	(–)	--
K (mEq/L)	4.6	4.9	--	--	--	5.2	5.9	5.2
BUN (mg/dL)	20.7	26.1	24.7	--	--	28.8	28.3	26.5
Cr (mg/dL)	0.84	0.90	0.92	--	--	1.09	0.99	0.91

BG: Blood glucose
HbA_{1c}: Haemoglobin A_{1c}
K: Potassium
BUN: Blood Urea Nitrogen
Cr: Creatinine

2 Gefitinib

Brand Name (name of company)	Iressa Tablets 250 (AstraZeneca K.K.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Inoperable or recurrent non-small cell lung cancer

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis, hepatic function disorder, jaundice: Hepatitis, hepatic function disorder with increases in AST (GOT), ALT (GPT), LDH, γ-GTP, Al-P, and bilirubin etc., or jaundice may occur. Patients should be carefully monitored by conducting liver function tests once every 1 to 2 months or depending on the condition of patients, etc. If sever changes in liver function test values are observed, appropriate measures such as drug discontinuation should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to July 4, 2006) (events for which a causality to the drug could not be denied)
- Hepatitis, jaundice: 9 cases (of which 1 had a fatal case)

The number of patients treated with Gefitinib estimated by MAH: approximately 2400 new-prescription patients, approximately 6800 refill patients
(The number of new-prescription and refill patients as of June 2006, which represents for those who were newly prescribed the drug between April and June 2006 and who had a refill of the drug by the end of June 2006, respectively.)
Marketed in Japan in: July 2002

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Squamous cell carcinoma of lung (none)	250 mg 56 days	**Hepatitis** Approx. 18 months before administration: Non small cell lung cancer (Squamous cell carcinoma, $T_1N_3M_1$) was diagnosed. Chemotherapy was performed. On day 1 of administration: Gefinitib was started as 3rd line therapy. On day 56 of administration (day of discontinuation): Gefinitib was discontinued due to progressive disease (PD). The patient developed hepatic function disorder, and AST (GOT) and ALT (GPT) were 750 IU/L and 765 IU/L, respectively. 1 day after discontinuation: The hepatic dysfunction disorder was aggravated with AST (GOT) of 1580 IU/L and ALT (GPT) of 1180 IU/L. Emergency hospitalization. 2 days after discontinuation: Further aggravation was noted with increase in AST (GOT) of 2180 IU/L and ALT (GPT) of 1520 IU/L. Prednisolone was started. 28 days after discontinuation: The hepatic function disorder showed a tendency toward improvement. Outcome: improved	Company report
	Concomitant medications: none				

Clinical Laboratory Values

	29 days before administration	On day 5 of administration	On day 56 of administration (day of discontinuation)	2 days after discontinuation	5 days after discontinuation	12 days after discontinuation	28 days after discontinuation
AST (GOT) (IU/L)	14	17	750	2180	234	49	26
ALT (GPT) (IU/L)	7	9	765	1520	599	131	27
LDH (IU/L)	152	162	692	1497	246	179	237
Al-P (IU/L)	--	194	287	331	305	237	212
γ-GPT (IU/L)	--	13	86	109	128	134	120
Total bilirubin (mg/dL)	0.5	0.4	1.1	2.2	1.2	1.0	0.9

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
Al-P: Alkaline Phosphatase
γ-GPT: γ-Glutamyltranspeptidase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 50s	Lung adenocarcinoma (none)	250 mg 12 days	**Jaundice** Approx. 6 months before administration: Abnormal chest X-ray was observed. The patient was diagnosed with lung adenocarcinoma [$cT_1N_1M_1$, stage IV (bone metastases)]. Approx. 3 months before administration: The patient underwent chemotherapy with gemcitabine hydrochloride and carboplatin (a total of 3 cycles). Liver disorder [AST (GOT), ALT (GPT) in the 100 IU/L level] was noted, but eventually improved. Approx. 1 month before administration: The patient developed concomitant carcinomatous pericarditis and underwent pericardial drainage. On day 1 of administration: Gefinitib was started. On day 4 of administration: The patient developed liver disorder. On day 12 of administration (day of discontinuation): Gefinitib was discontinued. Liver protection therapy was continued, but liver disorder was not improved. There were no liver metastases. The total bilirubin and ammonia levels were gradually increased and the patient eventually went into liver failure. 12 days after discontinuation: The patient developed jaundice. 20 days after discontinuation: The patient developed ascites. 44 days after discontinuation: The patient was in coma. 46 days after discontinuation: The patient died of liver failure. Autopsy findings: hepatic and lung tissues only Hepatic: hepatocyte necrosis (hepatitis fulminant was suspected.) Lung: lymphangiosis carcinomatosa Outcome: death	Company report
	Concomitant medications: none				

Clinical Laboratory Values

	1 day before administration	On day 4 of administration	On day 12 of administration (day of discontinuation)	12 days after discontinuation	27 days after discontinuation	36 days after discontinuation	45 days after discontinuation
AST (GOT) (IU/L)	140	227	404	301	239	239	303
ALT (GPT) (IU/L)	80	104	228	142	71	94	186
Al-P (IU/L)	631	835	1331	1280	976	855	888
Total bilirubin (mg/dL)	1.7	1.5	2.1	3.2	9.4	15.6	28.2

AST: Asparate Aminotransferase ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase

2

Revision of PRECAUTIONS

(No. 182)

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 Notification dated October 27, 2006 (excluding those presented in "1. Important Safety Information" of this Bulletin), together with reference information.

1 <Antipyretics and analgesics, anti-inflammatory agents> Diclofenac Sodium (oral dosage form, suppository, rectal ointment)

[Brand Name] Voltaren Tablets, Voltaren Suppo 12.5 mg, 25 mg, and 50 mg (Novartis Pharma K.K.), Voltaren SR Capsules (Dojin Iyaku-Kako Co., Ltd.), Rectos 25 and 50 (Teikoku Medix Co., Ltd.) and others.

[Adverse Reactions (clinically significant adverse reactions)] Congestive heart failure, myocardial infarction
Cerebrovascular disorder

<Reference Information> Company report

2 <Psychotropics> Fluvoxamine Maleate

[Brand Name] Depromel Tablets 25 and 50 (Meiji Seika Kaisha Ltd.), Luvox Tablets 25 and 50 (Solvay Seiyaku K.K.)

[Important Precautions] Sleepiness and consciousness disturbed such as depressed level of consciousness/ loss of consciousness may occur. Patients should be advised to refrain from engaging in potentially hazardous activities such as driving a car and operating machines.

[Adverse Reactions (clinically significant adverse reactions)] **Consciousness disturbed:** Consciousness disturbed such as depressed level of consciousness/loss of consciousness may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

3 <Antihypertensives> Urapidil

[Brand Name] Ebrantil 15 and 30 (Kaken Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder:** Hepatic function disorder with a marked increase in AST (GOT), ALT (GPT), γ-GTP, or Al-P etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Miscellaneous metabolism agents>

4 Alendronate Sodium Hydrate (oral dosage form) Sodium Risedronate Hydrate

[Brand Name] Fosamac Tablets 5 mg and 35 mg (Banyu Pharmaceutical Co., Ltd.), Bonalon Tablet 5 mg and 35 mg (Teijin Pharma Limited)
Actonel Tab. 2.5 mg (Ajinomoto Co., Inc.), Benet Tablets 2.5 mg (Takeda Pharmaceutical Company Limited)

[Important Precautions] Osteonecrosis/osteomyelitis of the jaw may occur in patients treated with bisphosphonates, including this drug. Most of the reported cases were associated with dental procedures such as tooth extraction or local infection. Also, the majority of cases were in cancer patients treated with intravenous bisphosphonate,but some have occurred in patients with osteoporosis taking oral bisphosphonate. Known risk factors for these diseases include malignant tumor, chemotherapy, corticosteroid therapy, radiation therapy, poor oral hygiene, and a history of dental procedure. Before starting administration, patients should be adequately advised on treatment with this drug. If any abnormalities are observed, patients should be advised to consult a dentist or dental surgeon immediately.

[Adverse Reactions (clinically significant adverse reactions)] **Osteonecrosis/osteomyelitis of the jaw:** Osteonecrosis/osteomyelitis of the jaw may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as drug discontinuation should be taken.

<Reference Information> Company report

<Miscellaneous metabolism agents>

5 Alendronate Sodium Hydrate (injectable dosage form) Incadronate Disodium

[Brand Name] Onclast Injection 5 mg and 10 mg (Banyu Pharmaceutical Co., Ltd.), Teiroc Injection 5 mg and 10 mg (Teijin Pharma Limited), Bisphonal Injection 10 mg (Astellas Pharma Inc.)

[Important Precautions] Osteonecrosis/osteomyelitis of the jaw may occur in patients treated with bisphosphonates, including this drug. Most of the reported cases were associated with dental procedures such as tooth extraction or local infection. Also, the majority of cases were in cancer patients treated with intravenous bisphosphonate,but some have also occurred in patients with osteoporosis taking oral bisphosphonate. Known risk factors for these diseases include malignant tumor, chemotherapy, corticosteroid therapy, radiation therapy, poor oral hygiene, and a history of dental procedure. Before starting administration, an appropriate dental examination should be performed as needed. During treatment with this drug, patients should avoid invasive dental procedures as much as possible. Patients should be adequately advised on treatment with this drug. If any abnormalities are observed, patients should be advised to consult a dentist or dental surgeon immediately.

[Adverse Reactions (clinically significant adverse reactions)] **Osteonecrosis/osteomyelitis of the jaw:** Osteonecrosis/osteomyelitis of the jaw may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as drug discontinuation should be taken.

<Reference Information> Company report

<Miscellaneous metabolism agents>

6 Etidronate Disodium

[Brand Name] Didronel Tablets 200 (Dainippon Sumitomo Pharma Co., Ltd.)

[Important Precautions] Osteonecrosis/osteomyelitis of the jaw may occur in patients treated with bisphosphonates. Most of the reported cases were associated with dental procedures such as tooth extraction or local infection. Also, the majority of cases

were in cancer patients treated with intravenous bisphosphonate,but some have also occurred in patients with osteoporosis taking oral bisphosphonate. Known risk factors for these diseases include malignant tumor, chemotherapy, corticosteroid therapy, radiation therapy, poor oral hygiene, and a history of dental procedure. Before starting administration, patients should be adequately advised on treatment with this drug. If any abnormalities are observed, patients should be advised to consult a dentist or dental surgeon immediately.

[clinically significant adverse reactions (similar drugs)] **Osteonecrosis/osteomyelitis of the jaw:** Osteonecrosis/osteomyelitis of the jaw has been reported to occur after administration of similar drugs. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as drug discontinuation should be taken

<Reference Information> Company report

<Miscellaneous metabolism agents>

7 Zoledronic Acid Hydrate Pamidronate Disodium

[Brand Name] Zometa Injection 4 mg (Novartis Pharma K.K.)
Aredia Injection 15 mg and 30 mg (Novartis Pharma K.K.)

[Important Precautions] Osteonecrosis/osteomyelitis of the jaw may occur in patients treated with bisphosphonates, including this drug. Most of the reported cases were associated with dental procedures such as tooth extraction or local infection. Also, the majority of cases were in cancer patients treated with intravenous bisphosphonate,but some have also occurred in patients with osteoporosis taking oral bisphosphonate. Known risk factors for these diseases include malignant tumor, chemotherapy, corticosteroid therapy, radiation therapy, poor oral hygiene, and a history of dental procedure. Before starting administration, an appropriate dental examination should be performed as needed. During treatment with this drug, patients should avoid invasive dental procedures as much as possible. Patients should be adequately advised on treatment with this drug. If any abnormalities are observed, patients should be advised to consult a dentist or dental surgeon immediately.

[Adverse Reactions (clinically significant adverse reactions)] **Osteonecrosis/osteomyelitis of the jaw:** Osteonecrosis/osteomyelitis of the jaw may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as drug discontinuation should be taken

<Reference Information> Company report

<Miscellaneous metabolism agents>

8 Tacrolimus Hydrate (capsules 0.5 mg, granules, injectable dosage form)

[Brand Name] Prograf Capsules 5 mg, Prograf Granules 0.2 mg and 1 mg, Prograf Injection 5 mg (Astellas Pharma Inc.)

[Adverse Reactions (clinically significant adverse reactions)] **Diabetes mellitus and hyperglycaemia:** Since diabetes mellitus may occur newly or may be aggravated, or hyperglycaemia may occur, patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as dose reduction or drug discontinuation should be taken.

<Reference Information> Company report

<Antineoplastics Plant extract preparations>

9 Docetaxel Hydrate

[Brand Name] Taxotere Injection (Sanofi-Aventis K.K.)

[Important Precautions] Patients may develop serious hypersensitivity to this drug. Careful observation should be made especially at the first and second administrations. Hypersensitivity symptom may occur within a few minutes of treatment. The patient's condition should be carefully observed with frequent monitoring for vital signs (e.g., blood

pressure, pulse rate) etc. for 1 hour after initiating administration. If serious hypersensitivity symptoms (dyspnoea, bronchospasm, blood pressure decreased, chest pressure sensation, rash etc.) are observed, administration should be discontinued immediately and appropriate measures should be taken. This drug should not be readministered in patients with serious hypersensitivity symptom.

<Reference Information> Company report

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10 <Antineoplastics-Miscellaneous> Imatinib Mesilate

[Brand Name] Glivec Tablets 100 mg, Glivec Capsules 100 mg (Novartis Pharma K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of December 1, 2006)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Aripiprazole / Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%	Otsuka Pharmaceutical Co., Ltd.	June 8, 2006
Solifenacin Succinate / Vesicare Tablets 2.5 mg and 5 mg	Astellas Pharma Inc.	June 8, 2006
Tolterodine Tartrate / Detrusitol Capsules 2 mg and 4 mg	Pfizer Japan Inc.	June 8, 2006
Amphotericin B / AmBisome for Intravenous Infusion 50 mg	Dainippon Sumitomo Pharma Co., Ltd.	June 20, 2006
Magnesium Sulfate/Glucose / Magsent Injection 100 mL	TOA Pharmaceuticals Co., Ltd.	June 20, 2006
Sertraline Hydrochloride / Jzoloft Tablets 25 mg and 50 mg	Pfizer Japan Inc.	July 7, 2006
Somatropin (Genetical recombination) / Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg[*1]	Pfizer Japan Inc.	July 26, 2006
Inulin / Inulead Inj.	FUJIYAKUHIN Co., Ltd.	August 22, 2006
Alendronate Sodium Hydrate / Fosamac Tablets 35 mg	Banyu Pharmaceutical Co., Ltd.	September 15, 2006
Alendronate Sodium Hydrate / Bonalon Tablet 35 mg	Teijin Pharma Limited	September 15, 2006
Itraconazole / Itrizole Oral Solution 1%	Janssen Pharmaceutical K.K.	September 15, 2006
Temozolomide / Temodal Capsules 20 mg and 100 mg	Schering-Plough K.K.	September 15, 2006
Budesonide / Pulmicort Respules 0.25 mg and 0.5 mg	AstraZeneca K.K.	September 15, 2006
Entecavir Hydrate / Baraclude Tablets 0.5 mg	Bristol Pharmaceuticals Y.K.	September 21, 2006
Cetrorelix Acetate / Cetrotide for Injection 0.25 mg and 3 mg	Nippon Kayaku Co., Ltd.	September 21, 2006
Manganese Chloride Tetrahydrate / Bothdel Oral Solution 10	Meiji Dairies Corporation	September 25, 2006
Gabapentin / Gabapen Tablets 200 mg, 300 mg, and 400 mg	Pfizer Japan Inc.	September 25, 2006
Olopatadine Hydrochloride / Patanol Ophthalmic Solution 0.1%	Alcon Japan Ltd.	October 5, 2006

Busulfan	Kirin Brewery Company, Limited	October 10, 2006[*2]
Busulfex Injection 60 mg		October 20, 2006[*3]
Fexofenadine Hydrochloride	Sanofi-Aventis K.K.	October 20, 2006
Allegra Tablets 60 mg[*4]		
Landiolol Hydrochloride	Ono Pharmaceutical Co., Ltd.	October 20, 2006
Onoact 50 for Injection		
Mozavaptan Hydrochloride	Otsuka Pharmaceutical Co., Ltd.	October 24, 2006
Physuline Tablets 30 mg		
Interferon Beta-1a (Genetical recombination)	Biogen Idec Japan Ltd.	November 6, 2006
Avonex IM Injection Syringe 30 μg		
Moxifloxacin Hydrochloride	Alcon Japan Ltd.	November 6, 2006
Vegamox Ophthalmic Solution 0.5%		
Pneumococcal Vaccine	Banyu Pharmaceutical Co., Ltd.	November 29, 2006
Pneumovax NP		
Bortezomib	Janssen Pharmaceutical K.K.	December 1, 2006
Velcade Injection 3 mg		

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