Pharmaceuticals and Medical Devices Safety Information

No. 269 May 2010

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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/, only available in Japanese language).

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

[Outline of Information]

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

To Pharmaceuticals and Medical Devices Safety Management Supervisor —Please use our e-mail alert service—

The Pharmaceuticals and Medical Devices Agency is providing a "Pharmaceuticals and Medical Devices Information E-mail Alert Service" (http://www.info.pmda.go.jp/info/idx-push.html, only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of PRECAUTIONS is issued. You are encouraged to register for and use the service.

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, it is mandatory for such providers 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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Project to Collect and Analyze Medical "Near-Miss" Incidents from Pharmacies

1. Introduction

Pharmacies are designated as "healthcare providers" under the "Act on the Partial Revision of the Medical Care Act and the other Relevant Acts to establish a quality healthcare providing system" (Act No. 84, June 2006, this is an unofficial translation). Accordingly, pharmacies should be responsible for developing the same safety assurance system as in hospitals, such as steps 1 through 4 which are listed below.

1. Development of safety management guidelines in pharmacies
2. Personnel training for safety management in pharmacies
3. Ensuring dispensing errors be reported to pharmacy managers
4. Development of operating procedures for drug safe use/management

The Japan Council for Quality Health Care (JCQHC) started the work for collecting medical "near-miss"/medication error cases to prevent medication error and promote medical safety since 2004. Of these incidents reported to JCQHC, about 30% are drug-related. Based on this, JCQHC has launched the "Project to Collect and Analyze Medical "Near-Miss" Incidents from Pharmacies" as a subsidiary project of MHLW. Registration of participating pharmacies and collection of information were started on April 1, 2009. This section introduces the Project.

2. The Project summary

(1) Objective

The objective of the Project is to further promote medical safety by encouraging pharmacies to share useful information for medical safety management and communication with the public. For this purpose, JCQHC collects and analyzes "near-miss" incidents, which might have resulted in health hazards, from pharmacies nationwide, and publishes information of the result.

(2) Participant registration

To participate in the Project, pharmacies need to register themselves via JCQHC website. Registration has been made by 2,244 pharmacies, which is less than 5% of existing pharmacies in Japan, as of March 31, 2010. Pharmacies with no incident to report so far may also register for participation in the Project. Registration is encouraged to raise awareness about safety management in pharmacies.

(3) Collection and analysis of “near-miss” incidents in pharmacies (Figure. 1)

Incidents related to drugs or special treatment materials, which occurred during daily activities in pharmacies, are subject to reporting. See below for examples. The term “medical procedure” in this section refers to any and all procedures related to medical practice, including sales of over-the-counter drugs.

i) An error in medical procedures was identified before the service is provided to the patient.
ii) Wrong medical procedures were taken but the patient was not affected or only minor treatment was required (minor treatment is limited to disinfection, wet pack or plaster, and analgesia, etc.).
iii) Wrong medical procedures were taken, and information about treatments taken is not available.

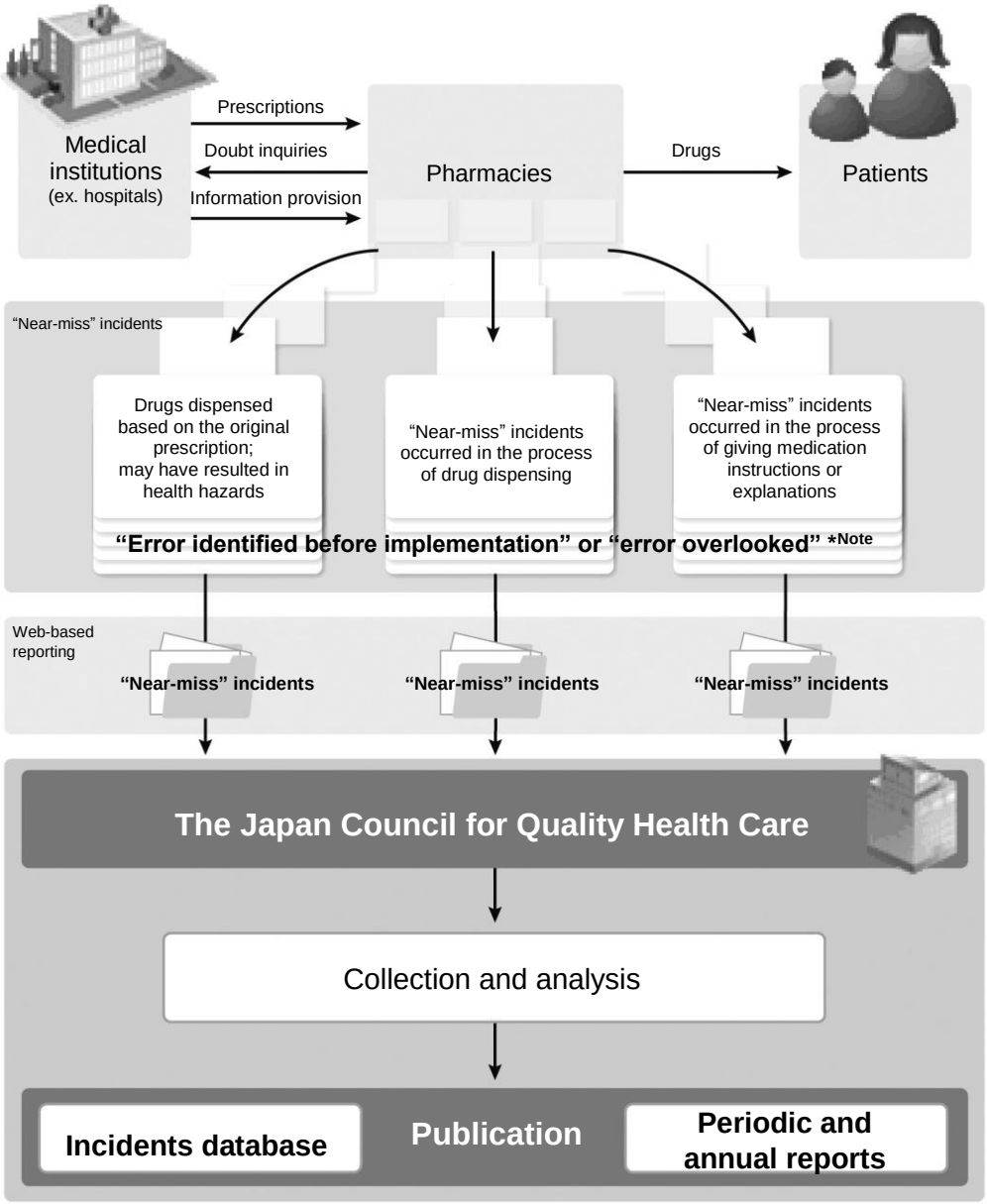
Such incidents are to be reported by individual pharmacies through the reporting page of JCQHC website within one month of awareness, in principle. Information securities are ensured using the SSL internet protocol. Collected incidents will be analyzed by JCQHC. Details of individual incidents are available on “Public Data Search” on JCQHC website (http://www.yakkyoku-hiyari.jcqhc.or.jp/). In addition, JCQHC publishes biannual summary reports and an annual report.

3. Summary report of the Project

On September 29, 2009, JCQHC published the first summary report of the Project including incidents reported between April 1 (the day of project commencement) and June 30, 2009. The second summary report, which includes incidents reported between July 1 and December 31, 2009, was published on March 24, 2010. The second summary report includes 1,285 “near-miss” incidents reported from 139 pharmacies; 1,177 incidents were related to “drug dispensing,” 99 were related to “doubt inquiries(gigishoukai in japanese)”, and 9 were related to “special treatment materials.” It also includes comprehensive and useful information for details of reported medication errors in "near-miss" cases which should be shared. These are 20 cases which are related oral drug dispensing, drug mix-up, and mix-up of dose/dosage form. All incident information to be shared is numbered so that details of individual incidents can be available by entering the number in the “Public Data Search” box on JCQHC website.

4. Closing Comments

Information about how to register with the Project and details of the collected incidents are available on JCQHC website. MHLW will evaluate and discuss the necessity of further safety measures based on incident information to be shared and analysis/assessment of reported incidents. It is hoped that the collected information will be shared by pharmacy managers, those responsible for safety management, and other staff members for promotion of medical safety within their pharmacies.



*Note
Of "error overlooked," the following incidents are to be reported:
1. The patient not affected or only minor treatment required (minor treatment is limited to disinfection, wet pack or plaster, and analgesia)
2. Information about influences on the patients is not available.

Figure 1. Activity Flow in the Project

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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 April 27, 2010.

[Brand Name]: Major product names are showed.

1 Clopidogrel Sulfate

Brand Name (name of company)	PLAVIX Tablets 25 mg (sanofi-aventis K.K)
Therapeutic Category	Blood and body fluid agents-Miscellaneous
Indications	○Suppression of recurrent ischemic cerebrovascular disorder (not including cardioembolic stroke) ○ Acute coronary syndrome (unstable angina pectoris, non ST segment elevation myocardial infarction) in patients who are to be managed with percutaneous coronary artery intervention PCI）

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

[Adverse Reactions (clinically significant adverse reactions)]

Pancytopenia including decreased platelets, agranulocytosis, and aplastic anaemia: Pancytopenia including decreased platelets, agranulocytosis, and aplastic anaemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin or increased urine myoglobin may be followed by serious renal disorder such as acute renal failure. If such symptoms are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 1, 2007 to January 29, 2010)

- Thrombocytopenia: 18 cases (no fatalities)
- Rhabdomyolysis: 3 cases (no fatalities)

The number of patients treated with this drug per year estimated by marketing authorization holder (MAH): approximately 650,000 (2009)

Marketed in Japan in: May 2006

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Angina pectoris (Gastritis, hypertension, supraventricular tachycardia)	75 mg for 14 days ↓ (administration suspended for 6 days) ↓ for 12 days	**Thrombocytopenia** Day 7 of administration: The patient had cold symptoms, arthralgia, general malaise. Day 13 of administration: The patient was admitted to the hospital for pyrexia of 38.5°C Day 14 of administration (day of discontinuation): Laboratory tests showed hepatic function disorder, pancytopenia, abnormal coagulation, and increased inflammatory reaction [AST (GOT) 180 IU/L, ALT (GPT) 89 IU/L, CRP 10.0 mg/dL, WBC 3000/mm^3, hemoglobin 12.6 g/dL, and platelet count $6\times10^4/mm^3$]. Administration of clopidogrel sulfate was discontinued. The patient's symptoms improved with anticoagulant and antibiotics. Disseminated intravascular coagulation (DIC) associated with infection was suspected (focus unknown). Coronary angiography (CAG) was performed due to aggravation of chest symptoms. Single-vessel disease of 90% stenosis was found in just proximal left anterior descending artery (LAD) #6. 7 days after discontinuation (day 1 of readministration): Early percutaneous coronary intervention (PCI) was considered necessary although the symptoms had been subsided after IV drip infusion. Clopidogrel sulfate 75 mg/day was resumed because the laboratory data had improved (WBC 7700/mm^3; platelet count $15\times10^4/mm^3$). Day 8 of readministration: Laboratory data was improved, and chest symptoms were stabilized. PCI was scheduled after 1 more week of monitoring. Hepatic function disorder and pancytopenia remitted. Day 11 of readministration: PCI was postponed due to pyrexia. Day 12 of readministration (day of discontinuation of readministration): Administration of clopidogrel sulfate was discontinued. Inflammatory reaction increased and mild abnormal coagulation and cytopenia was noted. Antibiotics and anticoagulants were resumed. Body temperature was tended to decrease. Inflammation was tended to improve. Pyrexia remitted. 11 days after discontinuation of readministration: AST (GOT) 23 IU/L, ALT (GPT) 33 IU/L, CRP 7.2mg/dL, WBC 6300/mm^3, hemoglobin 9.3g/dL. Platelet count decreased to $0.2\times10^4/mm^3$. Bleeding tendency was seen. Platelet transfusion was performed. Oral prednisolone and human immunoglobulin were given. (8 units of concentrated human red blood cells and 80 units concentrated human platelets for 5 days) 15 days after discontinuation of readministration: Platelet count was $3\times10^4/mm^3$, showing an improving tendency. No abnormal coagulation or aggravation of inflammatory reaction was seen. The dose of oral prednisolone was gradually decreased. 16 days after discontinuation of readministration: Emergency PCI (90% → 0% with bare-metal stent) was performed for ventricular tachycardia (VT) after chest pain. VT

				gradually subsided, and blood tests data was also improved. The patient was discharged from the hospital under the treatment with oral aspirin and warfarin potassium (hospitalization for 54 days). 36 days after discontinuation of readministration: Thrombocytopenia were in remission.
	Concomitant medications: aspirin, omeprazole, nifedipine, amlodipine besilate, valsartan, metildigoxin, trichlormethiazide			

Clinical Laboratory Values

	5 days before administration	Day 14 of administration (day of discontinuation)	7 days after discontinuation (day of readministration)	1 day after discontinuation of readministration	11 days after discontinuation of readministration	18 days after discontinuation of readministration	22 days after discontinuation of readministration
PLT ($\times 10^4/mm^3$)	18.8	6.0	15.0	19.9	0.2	9.3	19.6
WBC ($/mm^3$)	7200	3000	7700	3400	6300	5800	4200
RBC ($\times 10^4/mm^3$)	443	417	314	397	354	319	446

PLT: Platelet
WBC: White blood cell count
RBC: Red blood cell count

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 80s	Myocardial ischaemia, angina pectoris (Hyperlipidaemia, hypertension, reflux oesophagitis, cardiac failure, atrial fibrillation)	300 mg for 1 day ↓ 75 mg for 15 days	**Rhabdomyolysis** Day 1 of administration: The patient was scheduled to receive percutaneous coronary intervention (PCI) on the segment (1) – (2) for angina pectoris after coronary artery bypass graft. She received clopidogrel sulafate 300 mg/day as a loading dose. Day 2 of administration: Administration of clopidogrel sulfate 75 mg/day was started as a maintenance dose. Day 4 of administration: PCI (placement of 2 drug eluting stents [DESs]) was performed. Day 16 of administration (day of discontinuation): The patient was admitted to the hospital for severe myalgia of neck, shoulders, and lower extremities. She was diagnosed with rhabdomylysis based on CK (CPK) 3396 IU/L and troponin T (-). Administration of clopidogrel sulfate was discontinued. Pravastatin sodium was also discontinued. Day 11 after discontinuation: Rhabdomyolysis ramitted without further treatment. CK (CPK) 49 IU/L. Administration of cilostazol 200 mg/day and sarpogrelate hydrochloride 300 mg/day were started as alternative treatment.
	Concomitant medications: pravastatin sodium, furosemide, aspirin, valsartan, famotidine, digoxin, carvedilol, warfarin potassium			

Clinical Laboratory Values

	Day 5 of administration	Day 16 of administration (Day of discontinuation)	1 day after discontinuation	2 days after discontinuation	9 days after discontinuation
CK (CPK)(IU/L)	29	3396	2096	1166	42
AST (GOT)(IU/L)	16	120	106	91	22
ALT (GPT)(IU/L)	6	32	33	35	19
BUN (mg/dL)	—	—	—	—	13.9
Cr (mg/dL)	—	—	—	—	1.2

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)
ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)
BUN: Blood urea nitrogen

2 Sitagliptin Phosphate Hydrate, Vildagliptin, Liraglutide (Genetical Recombination), Alogliptin Benzoate

❶ Sitagliptin Phosphate Hydrate

Brand Name (name of company)	GLACTIV Tablets 25 mg (Ono Pharmaceutical Co., Ltd.) JANUVIA Tablets 25 mg (Banyu Pharmaceutical Co., Ltd.)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatment: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies (3) Thiazolidinedione along with diet and exercise therapies (4) Biguanide along with diet and exercise therapies

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

[Careful Administration] Patients on treatment with other agents <u>for</u> diabetes mellitus <u>(especially sulfonylurea)</u>

[Important Precautions] When administering this drug, patients should be thoroughly informed of possible hypoglycaemia and its treatment in advance. <u>In particular, the risk of hypoglycaemia increases when this drug is used in concomitant with sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with this drug to reduce the risk of sulfonylurea-induced hypoglycaemia.</u>

[Adverse Reactions (clinically significant adverse reactions)] **Hypoglycaemia**: Hypoglycaemia may occur when this drug is administered in concomitant with other drugs <u>for</u> diabetes mellitus (<u>5.3% with glimepiride, 0.8% with pioglitazone, 0.7% with metformin</u>). <u>Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated in concomitant use with sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with this drug.</u> Hypoglycaemia may also occur (1.0%) even if other agents <u>for</u> diabetes mellitus are not used. If symptoms of hypoglycaemia are observed, appropriate measures such as taking sugar-containing food should be taken.

<Reference Information> The number of adverse reactions (for which a causality to the drug could not be denied) reported between December 11, 2009 (markted in Japan) and April 19,

2010
• Hypoglycaemia: 25 cases (no fatalities)
The number of patients treated with this drug estimated by the MAH: approximately 230,000 (from the initial marketing to April 23, 2010)
Marketed in Japan in: December 2009

❷ Vildagliptin

Brand Name (name of company)	Equa Tablets 50 mg（Novartis Pharma K.K.）
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatment: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies

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

[Careful Administration] Patients on treatment with sulfonylurea

[Important Precautions] When administering this drug, patients should be thoroughly informed of possible hypoglycaemia and its treatment in advance. In particular, the risk of hypoglycaemia may increase when this drug is used in concomitant with sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with this drug to reduce the risk of sulfonylurea-induced hypoglycaemia.

[Adverse Reactions (clinically significant adverse reactions)] **Hypoglycaemia**: Hypoglycaemia may occur related to administration of this drug. Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated in concomitant use of other DPP-4 inhibitors and sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with this drug. If symptoms of hypoglycaemia are observed, appropriate measures such as taking sugar-containing food should be taken.

❸ Liraglutide (Genetical Recombination)

Brand Name (name of company)	VICTOZA Subcutaneous Injection 18mg (Novo Nordisk Pgarma Ltd.)
Therapeutic Category	Hormones-Miscellaneous
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatment: (1) Diet and exercise therapies alone (2) Sulfonylurea along with diet and exercise therapies

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

[Careful Administration] Patients on treatment with sulfonylurea

[Important Precautions] When administering this drug, patients should be thoroughly informed of possible hypoglycaemia and its treatment in advance. The incidence of hypoglycaemia increases when using this drug in concomitant with oral antidiabetics, compared with liraglutide monotherapy. Periodic blood glucose measurement should be conducted. In particular, the risk of hypoglycaemia may increase when this drug is used in concomitant with sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with this drug to reduce the risk of sulfonylurea-induced hypoglycaemia.

[Adverse Reactions (clinically significant adverse reactions)]

Hypoglycaemia: Hypoglycaemia and its symptoms (e.g, feelings of weakness, malaise, severe hunger, cold sweat, facial pallor, palpitations, tremor, headache, diziness, queasy, paraesthesia) may occur. The incidences of these symptoms especially increase when this drug is used in concomitant with sulfonylurea.
If symptoms of hypoglycaemia occur, caution should be exercised and this drug or conccurrent oral antidiabetics should be temporally discontinued or reduced in dosage.
Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated in concomitant use of other DPP-4 inhibitors and sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with this drug.
If symptoms of hypoglycaemia are observed, sucrose should be administered in general. If symptoms of hypoglycaemia are observed in concomitant use with α-glucosidase inhibitors, glucose should be administered.

❹ Alogliptin Benzoate

Brand Name (name of company)	NESINA Tablets 6.25 mg (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Antidiabetic agents
Indications	Type 2 diabetes mellitus To be used only when the patient does not sufficiently respond to one of the following treatment: (1) Diet and exercise therapies alone (2) α-glucosidase inhibitor along with diet and exercise therapies

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

[Important Precautions] Symptoms of hypoglycaemia may occur in patients treated in concomitant use with this drug or other antidiabetics. Patients should be thoroughly informed of possible symptoms of hypoglycaemia and its treatment to raise awareness before starting concomitant use with alogliptin and other antidiabetics. Clinical efficacy and safety of concomitant use of alogliptin and sulfonylurea have not been established; however, risks of hypoglycaemia may increase in concomitant use of DPP-4 inhibitor and sulfonylurea. Dose reduction of sulfonylurea should be considered when used in concomitant with a DPP-4 inhibitor to reduce the potential risks of hypoglycaemia.

[Adverse Reactions (clinically significant adverse reactions)] Symptoms of hypoglycaemia may occur. This drug should be administered while carefully monitoring the patient's condition. If symptoms of hypoglycaemia occur, caution should be exercised and the drug or concomitant oral antidiabetics should be temporarily discontinued or the dose should be reduced. Serious hypoglycaemia followed by loss of consciousness has been reported in patients treated in concomitant use of other DPP-4 inhibitors and sulfonylurea. If symptoms of hypoglycaemia are observed in association with administration of this drug, sucrose should be administered in general. If symptoms of hypoglycaemia are observed in concomittant use with α-glucosidase inhibitors, glucose should be administered.

Case Summary

<Sitagliptin Phosphate Hydrate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Type 2 diabetes mellitus (Diabetic nephropathy, diabetic neuropathy, hyperlipidaemia, urinary tract infection)	50 mg for 21 days	**Hypoglycaemia** Day 1 of administration: The patient had been treated with glimepiride (3 mg daily, QD, in the morning) and voglibose [(0.2mg TID (0.6 mg daily)) on an outpatient basis. Sitagliptin was added due to loss of control of blood sugar (HbA_{1c} 8.3%; blood glucose level 374 mg/dL). Serum creatinine 0.98mg/dL. Day 20 of administration: The patient had not been feeling well since the previous day. She could barely eat dinner. Day 21 of administration (day of discontinuation): The patient was still not feeling well in the morning and could hardly eat breakfast (had tea only). She took her medications as usual and went to her room. About an hour later she was still in her room. About 7 hours later her family found her unconscious in her room. About 8 hours later the patient was taken to the hospital by ambulance. Her level of consciousness according to the JCS (Japan Coma Scale) was III-200. She had respiratory discomfort and was snoring. No quadriplegia was noted. The results of the blood test showed hypoglycaemia (blood glucose level, 24 mg/dL). Mild inflammation was found (WBC, 16400/mm^3; CRP, 10.82 mg/dL).No brain attack was noted. Lactated Ringer's solution 500 mL and 50% glucose solution 40 mL were administered intravenously for hypoglycaemia. About 8 hours later, blood glucose level increased to 278 mg/dL. The patient regained consciousness and was able to speak. She was later transferred to another hospital for inpatient care at the discretion of the emergency physician. She was hospitalized for 10 days. Examinations upon admission showed concomitant urinary tract infection. She stated that she had continued her medications although she had been sick for several days prior to the onset of hypoglycaemia and did not take food regularly. Serum creatinine was 0.74 mg/dL. 8 days after discontinuation: The patient visited the hospital for periodic outpatient consultation for the first time after discharge. It was considered that the patient had completely recovered from hypoglycaemia without sequela because her condition seemed normal. Administration of voglibose was discontinued. Treatment was resumed with sitagliptin and half the previous dose of glimepiride.
	Concomitant medications: glimepiride, voglibose, epalrestat, telmisartan/hydrochlorothiazide, alprazolam, ethyl icosapentate, famotidine, mecobalamin, brotizolam, letrozole			

<Sitagliptin Phosphate Hydrate>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Diabetes mellitus (sequelae of cerebral infarction, hypertension)	50 mg for 37 days ↓ 25 mg for 40 days	**Hypoglycaemic coma** 25 days before administration: The patient started receiving voglibose 0.3 mg×3 and glimepiride 1.5 mg. Blood glucose level 186 mg/dL, HbA_{1c} 6.3%, BUN 26 mg/dL, and serum creatinine 1.5 mg/dL. Day 1 of administration: Administration of voglibose was discontinued. Sitagliptin 50 mg was started. Day 38 of administration: The dose of glimepiride was increased to 3.0 mg, and the dose of sitagliptin was reduced to 25 mg. Blood glucose level (fasting) was 186 mg/dL and HbA_{1c} was 5.9%. Day 53 of administration: Blood glucose level 199 mg/dL, BUN 30 mg/dL, serum creatinine 1.5 mg/dL. Day 66 of administration: Blood glucose level 123 mg/dL, HbA_{1c} 5.7%. Day 77 of administration (day of discontinuation): The patient started to feel groggy in the evening and was taken to another hospital by ambulance 2 hours later. Level of consciousness was unknown (whether CT or MRI was performed also unknown). Blood glucose level was around 40 mg/dL. Administration of sitagliptin and glimepiride were discontinued. The patient's condition improved with glucose injection. Blood glucose level improved to 110 mg/dL late at night. She regained consciousness and was sent home. 1 day after discontinuation: The blood glucose level 97 mg/dL. 15 days after discontinuation: The blood glucose level 202 mg/dL.
	Concomitant medications: glimepiride, clopidogrel sulfate, amlodipine besilate, aspirin, candesartan cilexetil			

3 Tacrolimus Hydrate (oral dosage form, injectable dosage form)

Brand Name (name of company)	Prograf Capsules 0.5 mg (Astellas Pharma Inc.)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	1. Prophylaxis of organ rejection in allogeneic kidney, liver, heart, lung, and pancreas transplants 2. Prophylaxis of rejection and graft-versus-host disease after bone marrow transplantation. 3. Myasthenia gravis (only for Prograf Granules 0.2 mg and 1 mg, Prograf Capsules 0.5 mg and 1 mg) 4. Rheumatoid arthritis (limited to the cases in which conventional therapy is not sufficiently effective; only for Prograf Capsules 0.5 mg and 1 mg) 5. Lupus nephritis (for which steroids are not sufficiently effective or inappropriate due to adverse reactions; only for Prograf Capsules 0.5 mg and 1 mg) 6. Refractory (steroid-resistant/steroid-dependent) active ulcerative colitis (limited to moderate-to-severe cases; only for Prograf Capsules 0.5 mg, 1 mg, and 5 mg)

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

[Important Precautions] Hypertension may occur. Periodic blood pressure measurement should be conducted. If blood pressure is increased, appropriate measures, such as treatment with antihypertensives, should be taken.

[Adverse Reactions (clinically significant adverse reactions)]

Central nervous system disorder including reversible posterior leukoencephalopathy syndrome and hypertensive encephalopathy: Central nervous system disorder such as reversible posterior leukoencephalopathy syndrome and hypertensive encephalopathy may occur. If symptoms such as generalized convulsion, disturbances in consciousness, confusion, language abnormality, visual disturbance, and paralysis occurs, neurological examination and imaging diagnosis with CT and MRI should be taken. In addition, this drug should be reduced in dosage or discontinued, and appropriate measures, such as a control of blood pressure and administration of anticonvulsants, should be taken.

<Reference Information> The number of reported adverse reactions (for which a causality to the drug could not be denied)for the past 3 years (April 1, 2007 to March 29, 2010)

• Reversible leukoencephalopathy syndrome or hypertensive encephalopathy: 16 cases (no fatalities)

The number of patients treated with this drugs per year estimated by MAH: approximately 45,000 (2009)

Marketed in Japan in: June 1993

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female Under age of 10	Juvenile rheumatoid arthritis (none)	2 mg for 56 days	**Tacrolimus encephalopathy** Approx 9 months before administration: The patient was admitted to a nearby hospital for persistent hyperthermia. 278 days before administration: The patient was diagnosed with juvenile rheumatoid arthritis (systemic) based on persistently elevated WBC counts and CRP. 265 days before administration: The patient started prednisolone (PSL) 19 mg for treatment of juvenile rheumatoid arthritis. Body temperature tended to decrease. 257 days before administration: After PSL dose reduction, the patient was admitted to the hospital for pyrexia, generalised erythema, and hepatic function disorder. Bone marrow examination showed haemophagocytosis. The patient was diagnosed as having concurrent haemophagocytic syndrome. Date unknown: The patient's symptoms remitted with combination therapy of PSL and cyclosporine A (CyA), She was discharged from the hospital. 35 days before administration: CyA dose had been decreased for about 2 months. The patient was admitted to the hospital again for relapse of juvenile rheumatoid arthritis (systemic). 26 days before administration: Treatment was started with PSL, continuous CyA, and methotrexate 2.5 mg/week. Day 1 of administration: Remittent fever continued. The patient received m-PSL pulse therapy. Administration of CyA was discontinued. Tacrolimus hydrate 2 mg was started. Day 2 of administration

				Blood concentration of tacrolimus hydrate was 16.1 ng/mL Day 33 of administration: The patient's symptoms were in remission. She was discharged from the hospital. Day 41 of administration: Blood concentration of tacrolimus hydrate was 6.3 ng/mL Day 56 of administration (day of discontinuation) Loss of consciousness and cyanosis occurred. The patient was admitted to the hospital. Clonic convulsion of extremities occurred 5 minutes after admission. Diazepam was administered. Clonic convulsion of extremities occurred 20 minutes after admission. Diazepam was administered. Treatments with continuous drip infusion of midazolam and concentrated glycerin/fructose×3 were started. Administration of tacrolimus hydrate was discontinued. 1 day after discontinuation: The patient regained consciousness. Administration of concentrated glycerin/fructose was discontinued. 2 days after discontinuation: Brain diffusion-weighted MRI showed a high-intensity signal in the occipital lobe, and thus the patient was diagnosed with tacrolimus encephalopathy. She was found to be temporarily blind (cortical blindness was diagnosed.). 3 days after discontinuation: The patient became restless. 4 days after discontinuation: Administration of carbamazepine was started. 6 days after discontinuation: Restlessness disappeared. Administration of midazolam was discontinued. 12 days after discontinuation: The patient started to see light. 17 days after discontinuation: The patient gradually regained her vision. 30 days after discontinuation: Rash appeared and spread all over her body (carbamazepine-induced eruption was suspected). 31 days after discontinuation: Administration of carbamazepine was discontinued. Sodium valproate was started. 48 days after discontinuation: The patient's symptoms remitted. She was discharged from the hospital. Tacrolimus encephalopathy rimitted. The dose of PSL was gradually decreased after discharge.
	Concomitant medications: prednisolone, methotrexate, famotidine, alfacalcidol, fluconazole, sulfamethoxazole/trimethoprim			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 40s	Prophylaxis against graft versus host disease (Acute lymphocytic leukaemia, graft versus host disease)	0.2 mg IV drip infusion for 69 days ↓ 10 mg Oral for 73 days	**Leukoencephalopathy** Approx 11 months before administration: The patient developed acute lymphocytic leukaemia. 7 days before administration: Total body radiation therapy (12 Gy, 7 to 5 days before administration) was performed as pretreatment for bone marrow transplantation. Day 1 of administration: Tacrolimus hydrate 0.2 mg (IV drip infusion) was started to prevent graft versus host disease after bone marrow transplantation. Day 2 of administration: Bone marrow transplantation was

				performed. Day 3 of administration: Blood concentration of tacrolimus hydrate was 12.7 ng/mL Approx 1 month after administration: Graft versus host disease occurred. Day 53 of administration: Administration of mycophenolate mofetil 1500 mg was started for treatment of graft versus host disease. Day 70 of administration: IV tacrolimus hydrate was switched to oral tacrolimus hydrate 10 mg. Day 87 of administration: Thrombotic microangiopathy occurred. Blood concentration of tacrolimus hydrate was 13.2 ng/mL. Date unknown: Aspergillosis occurred. Day 101 of administration: Administration of amphotericin B was started for treatment of aspergillosis (from Day 101 of administration to 8 days after discontinuation). Day 128 of administration: Blood pressure increased (160mmHg). Headache ocurred. Day 139 of administration: Headache was gradually aggravated, and the patient requested a detailed examination. Blood concentration of tacrolimus was 8.5 ng/mL Day 140 of administration: Administration of prednisolone 10 mg was started for treatment of graft versus host disease. Day 141 of administration: MRI was performed. The patient was diagnosed with Leukoencephalopathy. Day 142 of administration (day of discontinuation): Administration of tacrolimus hydrate was discontinued. Blood concentration of tacrolimus hydrate was 9.6 ng/mL. Gradual decrease of blood concentration of tacrolimus hydrate was attempted. 5 days after discontinuation: Blood concentration of tacrolimus hydrate was 3.5 ng/mL. 9 days after discontinuation: Blood concentration of tacrolimus hydrate was below the lower detection limit. Date unknown: Headache improved. 13 days after discontinuation: MRI showed improvement of demyelination and local oedema in the vertex. Administration of mycophenolate mofetil and prednisolone were discontinued. 18 days after discontinuation: The patient recovered from leukoencephalopathy. Thrombotic microangiopathy and aspergillosis were in remission.
	Concomitant medications:mycophenolate mofetil, ursodeoxycholic acid, prednisolone, teprenone, sulfamethoxazole/trimethoprim, nifedipine, liver Extract/flavin adenine dinucleotide, sucralfate, povidone-iodine, famotidine, levofloxacin hydrate, hydrocortisone, sodium chloride, diazepam, lansoprazole, hydrocortisone sodium phosphate, brotizolam, vancomycin hydrochloride, glycyrrhizin/glycine/cysteine			

3

Revision of PRECAUTIONS

(No.216)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised in according to the Notifications dated April 27, 2010 (excluding those presented in "2. Important Safety Information" in this Bulletin).

[Brand Name]: Major product names are showed.

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1 **<Digestive organ agents-Miscellaneous>**

Infliximab (Genetical Recombination)

[Brand Name] REMICADE for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corp.)

[Important Precautions] Malignant tumor such as malignant lymphoma were reported in a three-year follow-up survey after a clinical study. It is reported that long-term treatment with immunosuppressants may increase the risks of infection and malignant lymphoma in patients with chronic inflammatory disease. Malignant tumors such as malignant lymphoma were also reported in children and young adults treated with anti-TNFs including this drug. Whether malignant tumor is associated with this drug is unknown; however, caution should be exercised with the onset of malignant tumor.

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2 **<Miscellaneous metabolism agents-Miscellaneous>**

Adalimumab (Genetical Recombination)

[Brand Name] HUMIRA SC Injection 40 mg Syringe 0.8 mL (Abbott Japan Co., Ltd.)

[Important Precautions] The clinical study showed the incidence of malignant tumor such as malignant lymphoma were higher in the anti-TNFs group including this drug compared with the control group. It is reported that long-term treatment with immunosuppressants may increase the risks of infection and malignant lymphoma in patients with chronic inflammatory disease such as rheumatoid arthritis. Malignant tumors such as malignant lymphoma were also reported in children and young adults treated with anti-TNFs. Whether malignant tumor is associated with this drug is unknown; however, caution should be exercised with the onset of malignant tumor. Prior to administration of this drug, all patients (especially those previously receiving long-term treatment with immunosuppressants or PUVA therapy for psoriasis) should be screened for nonmelanoma skin cancer and continuously monitored during administration of this drug.

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3 **<Miscellaneous metabolism agents-Miscellaneous>**

Etanercept (Genetical Recombination)

[Brand Name] ENBREL 10 mg for S.C. Injection (Wyeth K.K.)

[Important Precautions] Malignant tumor such as malignant lymphoma were reported in a clinical study and its consecutive five-year long-term study. In general, it is reported that long-term treatment with immunosuppressants may increase the risks of infection and malignant lymphoma in patients with chronic inflammatory disease. Malignant tumors such as malignant lymphoma were also reported in children and young adults treated with anti-TNFs.

Whether malignant tumor is associated with this drug is unknown; however, caution should be exercised with the onset of malignant tumor.

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4 **<Psychotropics>**

Atomoxetine Hydrochloride

[Brand Name] Strattera capsule 5 mg (Eli Lilly Japan K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice, hepatic failure**: Hepatic function disorder with elevated liver function test results, jaundice, or hepatic failure may occur. Patients should be carefully monitored, and if any abnormality is observed, appropriate measures, such as discontinuing administration, should be taken.

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5 **<Psychotropics>**

Paroxetine Hydrochloride Hydrate

[Brand Name] PAXIL Tablets 10 mg (GlaxoSmithKline K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

[Use in Pregnant, Parturient And Nursing Women] **Pregnancy:** Pregnant women or women who may be pregnant should start the administration of this drug only if the potential benefits outweigh the risks. If pregnancy is confirmed during administration, discontinue administration or switch to an alternative treatment unless continuation of this drug is considered appropriate.

〔1) Overseas epidemiological studies showed the risk of congenital anomaly, especially cardiovascular abnormality (e.g. ventricular or atrial septal defect), in neonates of mothers who had been treated with this drug in the first trimester. One of the studies reported the incidence of cardiorvascular abnormality in neonates exposed to paroxetine was about 2% while that in unexposed neonates was about 1%.

2) It is reported that symptoms such as respiratory depression, apnoea, cyanosis, polypnoea, epileptiform attack, tremor, hypotonia or hypertonia, hyperreflexia, twitches, irritability, persistent crying, lethargy, somnolence, pyrexia, hypothermia, feeding disorder, vomiting, and hypoglycaemia occurred in neonates of mothers who had been treated with this drug in late pregnancy. Many of these symptoms occurred immediately after or within 24 hours of delivery. Some of these symptoms were reported as neonatal asphyxia or drug withdrawal symptoms.

3) Overseas epidemiological studies reported the risk of newborn persistent pulmonary hypertension was increased in neonates of mothers who had been treated with a selective serotonin reuptake inhibitor including this drug during their pregnancy. One of the studies showed the risk ratio for newborn persistent pulmonary hypertension in neonates who were born at or later than 34 gestation weeks was 2.4 (95% CI, 1.2 to 4.3) in those of mothers treated during their early pregnancy and 3.6 (95% CI, 1.2 to 8.3) in those of mothers treated during both early and late pregnancy.〕

<Reference Information>

Chambers, C.D., et al.: N.Engl.J.Med. 2006; 354(6): 579-587
Källén, B., et al.: Pharmacoepidemiol.Drug Saf. 2008; 17(8): 801-806

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6 **<Psychotropics>**

Sertraline Hydrochloride

[Brand Name] J ZOLOFT Tablets 25 mg (Pfizer Japan Inc.)

[Use in Pregnant, Parturient And Nursing Women] Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks.

〔The safety of this drug in pregnant women has not been established.

1) Withdrawal-like symptoms requiring prolonged hospitalization, respiratory support, and tube feeding were reported in neonates of mothers who had been treated with this

drug, other selective serotonin reuptake inhibitors (SSRIs), or serotonin/norepinephrine reuptake inhibitors (SNRIs) in late pregnancy. Reported clinical findings included respiratory distress, cyanosis, apnoea, seizure, temperature regulation disorder, feeding disorder, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, twitches, irritability, and persistent crying.
2) Overseas epidemiological studies reported the risk of newborn persistent pulmonary hypertension increased in neonates of mothers who had been treated with SSRIs including this drug during their pregnancy. One of the studies showed the risk ratio for newborn persistent pulmonary hypertension in neonates who were born at or later than 34 gestation weeks was 2.4 (95% CI, 1.2 to 4.3) in those of mothers treated during their early pregnancy and 3.6 (95% CI, 1.2 to 8.3) in those of mothers treated during both early and late pregnancy.〕

<Reference Information>

Chambers, C.D., et al.: N.Engl.J.Med. 2006; 354(6): 579-587
Källén, B., et al.: Pharmacoepidemiol.Drug Saf. 2008; 17(8): 801-806

<Psychotropics>

7 Fluvoxamine Maleate

[Brand Name]

DEPROMEL TABLETS 25 mg (Meiji Keika Kaisha, Ltd.), Luvox Tablets 25 mg (Abbott Seiyaku K.K.)

[Use in Pregnant, Parturient And Nursing Women]

Pregnant women or women who may be pregnant are not recommended to be administered this drug. If pregnancy is confirmed during administration, discontinuation of this drug is recommended.
〔The safety of this drug in pregnant women has not been established.
1) Symptoms such as dyspnoea, tremor, muscle tone abnormalities, convulsion, irritability, somnolence, disturbances in consciousness, vomiting, feeding disorder, and persistent crying were reported in neonates of mothers who had been treated with this drug in late pregnancy. Some of these symptoms may be reported as drug withdrawal symptoms.
2) Overseas epidemiological studies reported the risk of newborn persistent pulmonary hypertension increased in neonates of mothers who had been treated with other selective serotonin reuptake inhibitors (SSRIs) during their pregnancy. One of the studies showed the risk ratio for newborn persistent pulmonary hypertension in neonates who were born at or later than 34 gestation weeks was 2.4 (95% CI, 1.2 to 4.3) in those of mothers treated during their early pregnancy and 3.6 (95% CI, 1.2 to 8.3) in those of mothers treated during both early and late pregnancy.〕

<Reference Information>

Chambers, C.D., et al.: N.Engl.J.Med. 2006; 354(6): 579-587
Källén, B., et al.: Pharmacoepidemiol.Drug Saf. 2008; 17(8): 801-806

<Skeletal muscle relaxants>

8 Vecuronium Bromide
Rocuronium Bromide

[Brand Name]

Musculax Intravenous 4 mg (Shering-Plough K.K.)
Eslax Intravenous 25 mg/2.5mL (Shering-Plough K.K.)

[Important Precautions]

To reverse muscle relaxation associated with this drug, sugammadex sodium or anticholinesterases and atropine sulfate hydrate (to prevent adverse reactions associated with anticholinesterases) should be administered intravenously. If anticholinesterase is used, it should be used only after confirming the patient's recovery from muscle relaxation based on neuromuscular monitoring or spontaneous respiration
Read carefully "DOSAGE AND ADMINISTRATION" and "PRECAUTIONS" section in the package insert of the corresponding drugs.
When this drug needs to be readministrered following administration of sugammadex sodium, this drug should be administrated carefully with close monitoring of the patient's condition because appearance of the action of this drug may be delayed.

<Blood and body fluid agents-Miscellaneous>

9 Clopidogrel Sulfate

[Brand Name] PLAVIX Tablets 25 mg (sanofi-aventis K.K)

[Interaction] This drug is metabolized to active metabolites by CYP3A4, CYP1A2, CYP2C19, and CYP2B6.

[Interactions (contraindications for concomitant use)] Drugs that inhibit the drug-metabolizing enzyme (CYP2C19) (e.g. omeprazole)

[Other Precautions] An overseas clinical pharmacology study in healthy adult volunteers showed the inhibition of 5-μM ADP-induced platelet aggregation (platelet aggregation inhibition; %) after 24 hours of initial administration of this drug 300 mg. The results were obtained in 4 groups devided according to the metabolic capacity of CYP2C19; the ultrarapid metabolizer (UM) group, the extensive metabolizer (EM) group, the intermediate metabolizer (IM) group, and the poor metabolizer (PM) group, being 40 ± 21, 39 ± 28, 37 ± 21and 24 ± 26, respectively. Platelet aggregation inhibition (%) in the 4 groups after the consecutive 4 days of treatment with this drug 75 mg/day was 56 ± 13, 58 ± 19, 60 ± 18, and 37 ± 23, respectively. The platelet aggretation inhibitory action of this drug was decreased in the PM group.
An overseas clinical study and several observational studies in patients scheduled for percutaneous transluminal coronary angioplasty showed the incidences of cardiovascular events after treatment with this drug increased in the PM and IM groups of CYP2C19 compared with the EM group of CYP2C19.

<Reference Information>

Mega, J.L., et al.: N.Engl.J.Med. 2009; 360(4): 354-362
Collet, J.P., et al.: Lancet 2009; 373: 309-317
Sibbing, D., et al.: Eur.Heart J. 2009; 30(8): 916-922
Giusti, B., et al.: Am.J.Cardiol. 2009; 103(6): 806-811
Simon, T., et al.: N.Engl.J.Med. 2009; 360（4): 363-375

<Synthetic antibacterials >

10 Ofloxacin (oral dosage form)
Levofloxacin Hydrate (oral dosage form) (low-dose)

[Brand Name] TARIVID TABLETS 100 mg (Daiichi Sankyo Company, Limited.)
CRAVIT FINE GRANULES (Daiichi Sankyo Company, Limited.)

[Careful administration] Patients with myasthenia gravis

[Adverse Reactions (clinically significant adverse reactions)] Exacerbation of myasthenia gravis (Patients with myasthenia gravis may experience exacerbation of symptoms)

<Synthetic antibacterials >

11 Levofloxacin Hydrate (oral dosage form) (high-dose)

[Brand Name] CRAVIT FINE GRANULES 10%（Daiichi Sankyo Company, Limited.）

[Careful administration] Patients with myasthenia gravis

[Adverse Reactions (clinically significant adverse reactions)] **Exacerbation of myasthenia gravis**: Patients with myasthenia gravis may experience exacerbation of symptoms. Such patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

12 <Antivirals>
Darunavir Ethanolate

[Brand Name] PREZISTA Tablets 300 mg（JanssenPharmaceutical K.K.）

[Important Precautions] Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), and erythema multiforme have been reported in association with administration of this drug. In overseas clinical studies, rash, including events with unknown causality, occurred in 10.3% of patients treated with this drug. Rash requiring treatment discontinuation occurred in 0.5% of patients, severe rash with pyrexia and increased hepatic enzyme levels occurred in 0.4% of patients, and oculomucocutaneous syndrome (Stevens-Johnson syndrome) occurred in less than 0.1% of patients. In many cases, mild to moderate rash occurred within 4 weeks of treatment but achieved remission during the treatment. If severe rash occurs, administration should be discontinued immediately and appropriate measures should be taken.

[Adverse Reactions (clinically significant adverse reactions)] **Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, and erythema multiforme have been reported. If any abnormality are observed, administration should be discontinued immediately and appropriate measures should be taken.

13 <Biological preparations-Miscellaneous>
Peginterferon Alfa-2a (Genetical Recombination)

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

[Adverse Reactions (clinically significant adverse reactions)]

<Monotherapy of this product>
Pancytopenia, agranulocytosis, decreased white blood cells (< 2,000/μL), decreased platelets (< 50,000/μL), anaemia, pure red cell aplasia: Patients should be carefully monitored through periodic blood tests, etc. When reducing the dosage or discontinuing administration of this drug, refer to the section "Precautions of Dosage and Administration."

<Administration of this drug in combination with ribavirin>
Aplastic anaemia, pure red cell aplasia: Patients should be carefully monitored through periodic blood tests, etc. When reducing the dosage or discontinuing administration of this drug, refer to the section "Precautions of Dosage and Administration."

14 <Antivirals>
Ribavirin (Tablets)

[Brand Name] COPEGUS Tablet 200 mg (Chugai Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

<Administration of this drug in combination with peginterferon alfa-2a (genetical recombination)>
Aplastic anaemia, pure red cell aplasia: Patients should be carefully monitored through periodic blood tests, etc. When reducing the dosage or discontinuing administration of this drug, refer to the section "Precautions of Dosage and Administration."

15 <Vaccines>
Freeze-dried Japanese Encephalitis Vaccine (Cell Culture derived)

[Brand Name] JEBIK V（The Research Foundation for Microbial Diseases of Osaka University）

[Adverse Reactions (clinically significant adverse reactions)]

Anaphylactic shock, anaphylactoid symptoms: Anaphylactic shock or anaphylactoid symptoms (e.g, urticaria, dyspnoea, angioedema) may occur. Patients should be carefully monitored after vaccination. If any abnormalities are observed, appropriate measures should be taken.

Acute disseminated encephalomyelitis: Acute disseminated encephalomyelitis (ADEM) may occur. Pyrexia, headache, convulsion, movement disorder, and disturbances in consciousness generally occur wtihin several days to 2 weeks after vaccination. If ADEM is suspected, MRI for diagnosis of ADEM should be conducted and appropriate measures should be taken.

Convulsion: Convulsion may occur, generally immediately after or within several days of vaccination. If convulsion is suspected, patients should be carefully monitered and appropriate measures should be taken.

16 <Vaccines>
Recombinant Adsorbed Hepatitis B Vaccine (Yeast-derived)

[Brand Name] Bimmugen (The Chemo-Sero-Therapeutic Research Institute)

[Precautions of dosage and administration] An antibody test is preformed about 1 to 2 months after the third vaccination. In those who have not acquired HBs antibodies, additional vaccination should be considered.

<Reference>

CDC: MMWR 2006; 55(RR-16)
MHLW: "Hepatitis B (general Q&A), the third revised edition (April 2009)"

4

List of products subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of May 1, 2010)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL and 400 mg/16 mL Intravenous Infusion[*1]	Chugai Pharmaceutical Co., Ltd.	November 6, 2009
Amlodipine Besilate/ Atorvastatin Calcium Hydrate Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban	Pfizer Japan Inc.	December 2, 2009
Aprepitant EMEND Capsules 80 mg, 125 mg, EMEND Capsule Set	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate GLACTIV Tablets 25 mg, 50 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate JANUVIA Tablets 25mg, 50 mg, 100 mg	Banyu Pharmaceutical Co., Ltd.	December 11, 2009
Tadalafil Adcirca Tablets 20 mg	Eli Lilly Japan K.K.	December 11, 2009
Dexamethasone Cipecilate Erizas Capsule for Nasal Spray 400 μg	Nippon Shinyaku Co., Ltd.	December 11, 2009
Mesalazine ASACOL Tablets 400 mg	Zeria Pharmaceutical Co., Ltd.	December 16, 2009
Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells) Cervarix	GlaxoSmithKline K.K.	December 22, 2009
Vancomycin Hydrochloride	Toa Pharmaceutical	December 28, 2009

Vancomycin Ophthalmic Ointment 1%	Co., Ltd.	
Nitric Oxide INOflo for Inhalation 800ppm	Air Water Inc.	January 1, 2010
Tosufloxacin Tosilate Hydrate OZEX fine granules 15% for pediatric	Toyama Chemical Co., Ltd.	January 12, 2010
Budesonide / Formoterol Fumarate Hydrate Symbicort Turbuhaler 30 doses, 60 doses	AstraZeneca K.K.	January 13, 2010
Adalimumab (Genetical Recombination) HUMIRA SC Injection 40 mg Syringe 0.8 mL*2	Abbott Japan Co., Ltd.	January 20, 2010
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion100*3	Mitsubishi Tanabe Pharma Corp.	January 20, 2010
Nonacog Alfa (Genetical Recombination) BeneFIX Intravenous 500, 1000, 2000	Wyeth K.K.	January 20, 2010
Fentanyl Durotep MT Patch 2.1 mg, 4.2 mg, 8.4 mg, 12.6 mg, 16.8 mg*4	Janssen Pharmaceutical K.K.	January 20, 2010
Pramipexole Hydrochloride Hydrate BI•Sifrol Tablets 0.125 mg, 0.5 mg*5	Nippon Boehringer Ingelheim Co., Ltd.	January 20, 2010
Miriplatin Hydrate MIRIPLA for Intra-arterial Injection 70 mg	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Meropenem Hydrate Meropen Vial for IV Drip Infusion 0.25 g, 0.5g, Meropen Kit for Intravenous Drip Infusion 0.5 g*6	Dainippon Sumitomo Pharma Co., Ltd.	January 20, 2010
Peramivir Hydrate RAPIACTA Vial for IV Drip Infusion 150 mg, RAPIACTA Bag for IV Drip Infusion 300 mg	Shionogi & Co., Ltd.	January 27, 2010
Pneumococcal polysaccharide Conjugate Vaccine (adsorbed) Prevenar Suspension Liquid for S.C. Injection	Wyeth K.K.	February 24, 2010
Everolimus AFINITOR tablets 5 mg	Novartis Pharma K.K.	March 8, 2010
Rasburicase (Genetical Recombination) Rasuritek for I.V. Injection 1.5 mg, 7.5 mg	sanofi-aventis K.K	April 5, 2010
Olmesartan Medoxomil/Azelnidipine REZALTAS COMBINATION TABLETS LD, HD	Daiichi Sankyo Company, Limited.	April 16, 2010
Valsartan/Amlodipine Besilate EXFORGE Combination Tablets	Novartis Pharma K.K.	April 16, 2010
Vildagliptin Equa Tablets 50 mg	Novartis Pharma K.K.	April 16, 2010

Sugammadex Sodium Bridion Intravenous 200 mg, 500 mg	Schering-Plough K.K.	April 19, 2010
Duloxetine Hydrochloride Cymbalta Capsule 20 mg, 30 mg	Shionogi & Co., Ltd.	April 19, 2010
Latanoprost/Timolol Maleate Xalacom Combination Eye Drops	Pfizer Japan Inc.	April 20, 2010
Palonosetron Hydrochloride ALOXI I.V. Injection 0.75 mg	Taiho Pharmaceutical Co., Ltd.	April 22, 2010

*1: An additional indication for "treatment of patients with advanced or recurrent, inoperable non-squamous non-small cell lung cancer except for squamous cell carcinoma"
*2: An additional indication for "treatment of patients with psoriasis vulgaris or psoriasis arthropathica, which is not adequately responsive to conventional therapies"
*3: An additional indication for "treatment of patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis, which is not adequately responsive to conventional therapies"
*4: An additional indication for "analgesia of moderate to severe chronic pain cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (only in patients who switch from an opioid analgesic.)"
*5: An additional indication for "treatment of patients with moderate to severe idiopathic restless leg syndrome"
*6: An additional indication for "treatment of patients with febrile neutropenia"