Pharmaceuticals and Medical Devices Safety Information

No. 241 November 2007

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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).

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No. 241 November 2007

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

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

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

1

PMDA medical safety information is new posted on the Pharmaceuticals and Medical Devices Information Website

1. Introduction

The PMDA has been posting medical safety information, such as examples of medical incident reports relating to drugs and medical devices, on its pharmaceuticals and medical devices information website, and is now releasing additional "PMDA medical safety information" which will be presented hereafter. [The pharmaceuticals and medical devices information website (http://www.info.pmda.go.jp/) (hereinafter, "PMDInfoWeb")]

2. "PMDA Medical Safety Information"

The purpose of the "PMDA Medical Safety Information" site (http://www.info.pmda.go.jp/anzen_pmda/iryo_anzen.html) is as follows. Among the medical incident reports and adverse drug reaction/malfunction reports that have been collected to date, information on similar events that have been repeatedly reported and cases leading to notifications for revisions to package inserts are described on the site in an easily understandable manner and widely disseminated. Important reminders to encourage safe use of drugs and medical devices to health professionals are included, which have been considered based on the opinions of health professionals such as physicians, pharmacists, nurses, and clinical engineers, specialists such as those in the field of ergonomics, as well as industry organizations such as marketing approval holders of pharmaceuticals or medical devices.

Currently, the following items are listed on the "PMDA Medical Safety Information" site. Hereafter, the site will be updated with new medical safety information relating to drugs and medical devices as needed.

(1) **Points to note in case of obstruction of feeding tube**
This leaflet describes precautions to be taken using illustrations if a feeding tube becomes blocked in accordance with "Instructions to revise the package inserts of enteral feeding tubes etc." (PFSB/SD Notification No. 0615001 dated June 15, 2007).

(2) **Recall of resuscitation bags**
Resuscitation bags that are being voluntarily recalled are described by this leaflet using photographs to promote their easy identification by medical institutions etc. in accordance with "Voluntary recall of manual pulmonary resuscitators (Request)" (HPB/GAD Notification No. 0914001・PFSB/SD Notification No. 0914001, dated September 14, 2007).

3. Closing comments

The Medical Service Law and related legislation were revised to provide high quality medical services. It requires medical centres to appoint: 1) a safety control manager for drugs; and 2) a safety control manager for medical devices. We encourage you to utilize the information on PMDInfoWeb to improve medical safety at medical centres by safe use of drugs and medical devices.

2

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 September 21, 2007.

1 Amiodarone Hydrochloride (oral dosage form), Amiodarone Hydrochloride (injectable dosage form)

❶ Amiodarone Hydrochloride (oral dosage form)

Brand Name (name of company)	Ancaron Tablets 100 (Sanofi-Aventis K.K.) Amiodarone Hydrochloride Tablets 100 mg "SAWAI" (Medisa Shinyaku Inc.) Amiodarone Hydrochloride Tablets 100 mg "SANDOZ" (Sandoz K.K.)
Therapeutic Category	Antiarrhythmic agent
Indications	The treatment of the following life-threatening recurrent arrhythmias which have not responded to other available antiarrhythmics or when alternative agents could not be tolerated: - Ventricular fibrillation - Ventricular tachycardia - Atrial fibrillation with hypertrophic cardiomyopathy

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

[Important Precautions]

As this drug may increase cardiac pacing thresholds, it should be used with adequate caution in patients with permanent pacemakers or patients undergoing temporary pacing. In patients with pacemakers, pacing thresholds should be measured at appropriate intervals during treatment with the drug. If any abnormality is observed, the dose of the drug should be reduced or administration should be discontinued immediately.

If an arrhythmia intended to be treated by an implantable cardioverter defibrillator (ICD) occurs in a patient with an ICD, the arrhythmia may not detected due to the heart rate slowing effect of this drug, resulting in a loss of ICD therapy. When treatment with the drug is added or the dose of the drug is changed in patients with ICDs, these patients should be carefully monitored.

[Adverse Reactions (clinically significant adverse reactions)]

Pulmonary alveolar haemorrhage: Pulmonary alveolar haemorrhage may occur. Patients should be closely monitored. If any abnormal findings are observed, administration of this product should be discontinued and appropriate measures should be taken.

❷ Amiodarone Hydrochloride (injectable dosage form)

Brand Name (name of company)	Ancaron Injection 150 (Sanofi-Aventis K.K.)

Therapeutic Category	Antiarrhythmic agent
Indications	Emergency treatment of the following life-threatening arrhythmias refractory to other therapy: Ventricular fibrillation, and haemodynamically unstable ventricular tachycardia

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

[Other Precautions]

Elevated cardiac pacing threshold has been reported in Japan in patients with pacemakers who were orally treated with this drug. It has also been reported that in patients with an implantable cardioverter defibrillator (ICD) to treat arrhythmia, the arrhythmia went undetected due to the heart rate slowing effect of the drug, resulting in a loss of ICD therapy.

<Reference Information>

Nakae T, et al.: Heart 2004:36 (Suppl4) (in Japanese)
Matsuda H, et al.: Respiration and Circulation 2005:53 (9) (in Japanese)
Matsuda H, et al.: Heart 2005:37 (Suppl3) (in Japanese)

The number of adverse reaction cases over approx. the last 3 years (April 1, 2004 to August 22, 2007) (events for which a causality to the drug could not be denied)
- Elevated pacing threshold: 2 cases (no fatal case)
- Implantable defibrillator malfunction: 1 case (no fatal case)
- Pulmonary alveolar haemorrhage: 3 cases (no fatal case)

The annual number of users of the drug estimated by the relevant companies:
-Approximately 28000 patients (September 2006 to August 2007)
Marketed in Japan in:
-October 1992 (oral dosage form)
-June 2007 (injectable dosage form)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Ventricular tachycardia (hypertrophic cardiomyopathy, deep vein thrombosis, pneumonia bacterial)	200 mg 3 years and 3 days	**Pulmonary alveolar haemorrhage** On day 1 of administration: Administration of this drug was initiated due to sustained ventricular tachycardia. About 2 years and 11 months of administration: The patient had cold symptoms. On day 1096 of administration: Difficulty breathing developed. On day 1097 of administration: The patient visited an emergency room. Although pericardial effusion was not detected, left atrial enlargement and left ventricular hypertrophy were noticeable. There was bilateral pleural effusion (right>left). Hypertrophy of bronchovascular bundles and an infiltrative shadow in the lung parenchyma around it, with surrounding ground-glass opacity were noted in

				the middle lobe/the lingular segment/the lower lobes of the lungs. On day 1098 of administration: Antibiotics and methylprednisolone sodium succinate (3 days) were administered, resulting in temporary improvement of the lung fields. On day 1099 of administration: Amiodarone hydrochloride was discontinued. (day of discontinuation) 3 days after discontinuation: A slight increase in bilateral pleural effusion was observed. There was improvement of the infiltrative shadow in the lung parenchymas around the bronchovascular bundles observed in the lower lobes of both lungs. On the other hand, the infiltrative shadows in the middle lobe and the lingular segment had changed to ground-glass opacity, and ground-glass opacity appeared in the inner layer of the upper lobe. Conversely, ground-glass opacity observed in the periphery of the apex of the right lung had disappeared. Cardiomegaly had improved compared with the previous examination. 4 days after discontinuation: The patient was diagnosed with pulmonary alveolar haemorrhage by bronchoscopy. Interstitial pneumonia was unlikely. The patient was intubated for controlled mechanical ventilation due to worsening of respiratory status observed again after bronchoscopy. Steroid pulse therapy was initiated. 8 days after discontinuation: The patient’s condition improved after steroid pulse therapy and the patient was extubated. The patient’s respiratory condition remained stable thereafter. 11 days after discontinuation: There was an increase in bilateral pleural effusion. The ground-glass opacity seen in both lungs was still identifiable. Although there appeared to be some improvement in the upper lobe, there was little change as a whole. Cardiomegaly had progressed. Possible pulmonary oedema etc. was also suspected. 20 days after discontinuation: The patient had anorexia, repeated vomiting, and dehydration. Cardiac function worsened and blood pressure decreased occurred. 21 days after discontinuation: Notable improvement of the bilateral pleural effusion was observed. There were residual infiltrative and patchy shadows in the right lung. There was residual ground-glass opacity in both lungs which had improved compared with the previous examination. The infiltrative shadows were suggestive of

				pulmonary alveolar haemorrhage. There was no change in the cardiomegaly. A ventricular tachycardia attack occurred. 22 days after discontinuation: Resuscitation was attempted, but the patient died.
	Concomitant medications: furosemide, carvedilol, valsartan, cloxazolam, famotidine, cernitin pollen-extract, magnesium oxide, sennoside, warfarin potassium, procainamide hydrochloride, sulbactam sodium/ampicillin sodium, methylprednisolone sodium succinate			

Clinical Laboratory Values

	Day of administration		Days after discontinuation							
	1097	1098	1	4	5	7	9	11	16	22
WBC (/mm^3)	10700	7900	10000	7700	5000	8500	12000	10800	15100	3400
PLT ($\times 10^4/mm^3$)	18.9	17.0	20.7	19.2	16.1	14.6	19.7	9.4	9.8	6.9
PT-INR	2.63	—	2.39	1.26	1.42	1.27	1.32	1.20	1.10	—
CRP (mg/dL)	6.23	10.97	10.96	2.24	4.95	2.52	1.59	1.64	8.06	—
LDH (IU/L)	261	337	383	323	—	319	521	363	299	—

WBC: White Blood Cell

PLT: Platelet

PT-INR: Prothrombin Time-International Normalized Ratio

CRP: C-Reactive Protein

LDH: Lactate Dehydrogenase

3

Revision of PRECAUTIONS (No. 191)

(1) Drugs

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated September 7 and 21, 2007 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 <Antidotes>

Pralidoxime Iodide

[Brand Name] PAM Injection 500 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Important Precautions] Overestimation of blood glucose levels may occur when a patient is being treated with this drug. Information on the influence on blood glucose readings measured by blood glucose reagent test strips and a blood glucose meter should be obtained in advance from the relevant marketing authorisation holder. (Overestimation of blood glucose levels may occur when a patient is being treated with this drug, and a false high glucose reading can lead to the administration of a hypoglycaemic agent including insulin, followed by serious symptoms of hypoglycemia such as coma.)

2 <IVD (in vitro diagnostics)>

Accu-Chek Aviva Test Strips

[Warning]

WARNING

The following patients should not be treated with this product, since overestimation of blood glucose levels may occur. (A false high glucose reading can lead to the administration of a hypoglycaemic agent including insulin, followed by serious symptoms of hypoglycemia such as coma.)

- Patients receiving infusion therapy solutions etc. (note: overestimation of blood glucose levels occurs when a patient is receiving infusions containing maltose.)
- Patients receiving dialysis solution containing icodextrin
- Patients undergoing galactose tolerance test
- Patients undergoing xylose absorption test
- Patients receiving pralidoxime iodide

As a general rule, this product is intended for home use by diabetic patients for glucose monitoring.

[Precautions (interfering substances/drugs)] Pralidoxime iodide may cause overestimation of blood glucose level.

<Reference Information> Among blood glucose self-monitoring kits (only those using the enzyme glucose dehydrogenase and coenzyme pyroloquinoline quinone), falsely high glucose results were obtained with this product in a study of glucose determination in the presence of pralidoxime iodide, conducted by the company.

<IVD (in vitro diagnostics)>

3 Cyclic GB Sensor, LFS Quick Sensor, Ascensia Easyfill Sensor, Ascensia Autodisc Sensor, Glutest Sensor, Dia Sensor, G Sensor, Glutest Neo Sensor

[Warning]

WARNING

The use of this product should be avoided in the following types of patients, since overestimation of blood glucose results may occur. (Inappropriate administration of hypoglycaemic agents including insulin, based on a false high glucose reading can lead to serious symptoms of hypoglycemia such as coma.)

・Patients receiving pralidoxime iodide

[Precautions (interfering substances/drugs)] Pralidoxime iodide may cause overestimation of blood glucose results.

<Reference Information> Among blood glucose self-monitoring kits (excluding those using the enzyme glucose dehydrogenase method and coenzyme pyroloquinoline quinone), falsely high glucose results were obtained with this product in a study of glucose determination in the presence of pralidoxime iodide, conducted by the company.

<IVD (in vitro diagnostics)>

4 Blood glucose test kits，Blood glucose self-monitoring kits (excluding those listed in 2 and 3 above)

[Warning]

WARNING

Overestimation of blood glucose results may occur when a patient is being treated with pralidoxime iodide. Information on the influence on blood glucose readings in patients receiving pralidoxime iodide should be obtained from the relevant marketing authorisation holder in advance. [Overestimation of blood glucose results may occur when the patient is being treated with pralidoxime iodide and inappropriate administration of a hypoglycaemic agent including insulin based on a false high glucose reading can lead to serious symptoms of hypoglycemia such as coma.]

<Psychotropics>

5 Methylphenidate Hydrochloride

[Brand Name] Ritalin Tablets “Ciba,” 1% Ritalin Powder “Ciba” (Novartis Pharma K.K.)

[Contraindications] Patients with phaeochromocytoma

6 <Miscellaneous> Tiapride Hydrochloride

[Brand Name]	Gramalil Fine Granules 10%, Gramalil Tablets 25 mg and 50 mg (Astellas Pharma Inc.), etc.
[Contraindications]	Patients with prolactin-secreting pituitary tumor (prolactinoma)
[Careful Administration]	Patients with QT prolongation Patients who are likely to develop QT prolongation 1) Patients with marked bradycardia 2) Patients with hypokalaemia, etc.
[Adverse Reactions (clinically significant adverse reactions)]	**QT prolongation, ventricular tachycardia:** QT prolongation and ventricular tachycardia (including torsades de pointes) may occur. Patients should be carefully monitored, and if any abnormal findings occur, administration of this product should be discontinued and appropriate measures should be taken.

7 <Ophthalmic agents> Verteporfin

[Brand Name]	Visudyne for Intravenous Infusion 15 mg (Novartis Pharma K.K.)
[Precautions of Indications]	There is data showing that there is no statistically significant difference in efficacy (control of visual acuity reduced) between this drug and a placebo in patients with occult CNV (choroidal neovascularisation) or minimally classic CNV. Therefore, this drug should be used in these patients only when the expected benefits outweigh the possible risks.

8 <Thyroid and parathyroid hormone preparations> Liothyronine Sodium

[Brand Name]	5 mcg Thyronamin Tablets, 25 mcg Thyronamin Tablets (Takeda Pharmaceutical Company Limited)
[Adverse Reactions (clinically significant adverse reactions)]	Hepatic function disorder with marked elevations of AST (GOT), ALT (GPT), and γ-GTP, pyrexia, and malaise, and jaundice may occur. Patients should be carefully monitored, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.

9 <Miscellaneous> Finasteride

[Brand Name]	Propecia Tablets-0.2 mg and 1 mg (Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder:** Hepatic function disorder may occur. Patients should be carefully monitored and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.

<Vitamin B preparations>

10 Pyridoxal Phosphate, Pyridoxal Calcium Phosphate, Pyridoxine Hydrochloride

[Brand Name]	Pydoxal Tablets 10 mg, 20 mg, and 30 mg, Pydoxal Injection 10 mg and 30 mg (Chugai Pharmaceutical Co., Ltd.), etc. Aderoxal Powder (Zonnebod-seiyaku Inc.) Strong Aderoxin Powder (Zonnebod-seiyaku Inc.), Aderoxin Injection 10 mg (Toa Pharmaceutical Co., Ltd.), etc.
[Adverse Reactions (clinically significant adverse reactions)]	**Rhabdomyolysis:** If a high dose of the drug is administered to neonates and infants, rhabdomyolysis characterized by CK (CPK) elevation and blood and urine myoglobin increased may develop, which could lead to serious renal disorder such as acute renal failure. Patients should be carefully monitored, and if any abnormal findings are observed, administration should be discontinued immediately.
[Use in Children]	If a high dose of the drug is administered to neonates and infants, adverse reactions such as rhabdomyolysis, diarrhoea, vomiting, and hepatic function abnormal may occur. Therefore, the drug should be administered with care.

<Antidiabetic agents>

11 Miglitol

[Brand Name]	Seibule Tab. 25 mg, 50 mg, and 75 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Intestinal obstruction-like symptoms:** Abdominal distension and flatulence may occur and intestinal obstruction-like symptoms due to a build-up of air in the intestines may develop. Patients should be carefully monitored, and if such symptoms are observed, appropriate measures, such as discontinuing treatment, should be taken. **Hepatic function disorder, jaundice:** Hepatic function disorder with elevations of AST (GOT) and ALT (GPT) and jaundice may occur. Patients should be carefully monitored and if any abnormal findings occur, administration of this product should be discontinued and appropriate measures should be taken.

<Miscellaneous metabolism agents>

12 Etidronate Disodium

[Brand Name]	Didronel Tablets 200 (Dainippon Sumitomo Pharma Co., Ltd.)
[Important Precautions]	Bisphosphonates, including this product, may cause osteonecrosis of the jaw and osteomyelitis of the jaw. Most of the reported cases were related to dental procedures such as tooth extraction or local infections and were cancer patients on intravenous bisphosphonates, although such events have also been reported by patients with osteoporosis on oral bisphosphonates. The known risk factors are malignant tumor, chemotherapy, corticosteroid therapy, radiation therapy, poor

	oral hygiene, and a history of dental procedures, etc. Prior to the administration of this product, the patient should be fully informed and cautioned to consult a dentist or dental surgeon immediately if any abnormalities are found.
[Adverse Reactions (clinically significant adverse reactions)]	**Osteonecrosis of the jaw • Osteomyelitis of the jaw:** Osteonecrosis of the jaw and osteomyelitis of the jaw may develop. Patients should be carefully monitored and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.

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13 <Miscellaneous> Anastrozole

[Brand Name]	Arimidex Tablets 1 mg (AstraZeneca K.K.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with elevations of AST (GOT), ALT (GPT), Al-P, and γ-GTP and jaundice may occur. Patients should be carefully monitored through periodic hepatic function tests. If any abnormalities are found, appropriate measures, such as discontinuing treatment, should be taken.

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14 <Positive and gram-negative bacteria> Ceftriaxone Sodium

[Brand Name]	Rocephin Intravenous 0.5 g and 1 g, Rocephin Infusion Bag 1 g (Chugai Pharmaceutical Co., Ltd.), etc.
[Important Precautions]	The product must not be co-administered with calcium-containing IV solutions or continuous calcium-containing infusions. [Cases of fatal outcomes with ceftriaxone-calcium precipitation in the lung and kidneys in neonates co-administered this product and calcium-containing IV solution or continuous calcium-containing infusion via the same infusion line have been reported outside Japan. (See “Precautions in Use”)]
[Precautions in Use (incompatibility)]	It has been reported that changes such as turbidity occurred when mixed with calcium-containing IV solutions or continuous calcium-containing infusions. Therefore, the product should not be mixed with these solutions.

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(2) Medical Devices

This section presents details of revisions to the PRECAUTIONS section of package inserts of medical devices that have been revised according to the Notification dated September 7 and 21, 2007.

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1 Glucose meters for self-monitoring (only those using the glucose dehydrogenase method and coenzyme pyroloquinoline quinone) found to be affected by pralidoxime iodide in a study conducted by the manufacturer.

[Warning]

WARNING

The use of this device is contraindicated in the following types of patients since overestimation of blood glucose results may occur. [Inappropriate administration of a hypoglycaemic agent including insulin based on a false high glucose reading can lead to serious symptoms of hypoglycemia such as coma.]

- Patients receiving infusion therapy solutions etc. (Overestimation of blood glucose results occurs when the patient is being treated with solutions containing maltose.)
- Patients receiving dialysis solution containing icodextrin
- Patients undergoing galactose tolerance test
- Patients undergoing xylose absorption test
- Patients receiving pralidoxime iodide

As a general rule, this device is intended for home use by patients for glucose monitoring.

2 Glucose meters for self-monitoring (except for those listed in 1 above) and glucose analyzers etc. (only those using no reagents) found to be affected by pralidoxime iodide in a study conducted by the manufacturer.

[Warning]

WARNING

The use of this device is contraindicated in the following types of patients since overestimation of blood glucose results may occur. [Inappropriate administration of a hypoglycaemic agent including insulin based on a false high glucose reading can lead to serious symptoms of hypoglycemia such as coma.]

- Patients receiving pralidoxime iodide

3 Glucose meters for self-monitoring, glucose analyzers etc. (medical devices for measuring blood glucose levels) (except for those listed in 1 and 2 above)

[Warning]

WARNING

Overestimation of blood glucose results may occur when a patient is being treated with pralidoxime iodide. Information on the effect on blood glucose readings in patients receiving pralidoxime iodide should be obtained from the relevant marketing authorisation holder in advance. [Overestimation of blood glucose results may occur when a patient is being treated with pralidoxime iodide and inappropriate administration of a hypoglycaemic agent including insulin based on a false high glucose reading can lead to serious symptoms of hypoglycemia such as coma.]

4 Implantable cardioverter defibrillators

[Important Precautions] An additional or a change in dose of a concomitant medication may affect a patient's cardiac function. The detection criteria for tachycardia should be reassessed and a defibrillation test etc. should be performed to confirm that defibrillation effect has been achieved. [See "Interactions".]

5 Implantable cardioverter defibrillators (rate-based parameters for tachycardia detection models)

[Interactions (precautions for concomitant use)]

Medical device or drug	Clinical symptom and treatment	Mechanism and risk factor
Antiarrhythmic agents (Amiodarone hydrochloride, etc.)	・An additional or increased dose of an antiarrhythmic agent or a change of the drug may result in a loss of ICD therapy. Reassessment of the tachycardia detection rate of the ICD should be considered.	・Due to the heart rate slowing effect of an antiarrhythmic agent, the rate of arrhythmia to be treated may fall below the programmed tachycardia detection rate of the ICD.
	・An additional or an increased dose of an antiarrhythmic agent or a change of the drug may result in a loss of ICD therapy or no therapeutic effect. Reassessment of the defibrillation parameters of the ICD should be considered.	・Due to changes in an intracardiac electrogram waveform or defibrillation thresholds associated with an antiarrhythmic agent, arrhythmia to be treated may not be defibrillated appropriately by the ICD.

6 Implantable cardioverter defibrillators (interval-based parameters for tachycardia detection models)

[Interactions (precautions for concomitant use)]

Medical device or drug	Clinical symptom and treatment	Mechanism and risk factor
Antiarrhythmic agents (Amiodarone hydrochloride, etc.)	・An additional or an increased dose of an antiarrhythmic agent or a change of the drug may result in a loss of ICD therapy. Reassessment of the	・Due to the heart rate slowing effect of an antiarrhythmic agent, the interval of arrhythmia to be treated may exceed the programmed

	tachycardia detection interval of the ICD should be considered.	tachycardia detection interval of the ICD.
	・An additional or an increased dose of an antiarrhythmic agent or a change of the drug may result in a loss of ICD therapy or no therapeutic effect. Reassessment of the defibrillation parameters of the ICD should be considered.	・Due to changes in an intracardiac electrogram waveform or defibrillation thresholds associated with an antiarrhythmic agent, arrhythmia to be treated may not be defibrillated appropriately by the ICD.

4

List of products subject to Early Post-marketing Phase Vigilance

(As of November 1, 2007)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Pegvisomant (Genetical recombination) Somavert for s.c. Injection 10 mg, 15 mg, and 20 mg	Pfizer Japan Inc.	June 5, 2007
Salmeterol Xinafoate/Fluticasone Propionate Adoair 100 Diskus, 250 Diskus, and 500 Diskus	GlaxoSmithKline K.K.	June 8, 2007
Ciclesonide Alvesco 50 μg Inhaler 112 puffs, 100 μg Inhaler 112 puffs, and 200 μg Inhaler 56 puffs	Teijin Pharma Limited	June 8, 2007
Fondaparinux Sodium Arixtra Injection 1.5 mg and 2.5 mg	GlaxoSmithKline K.K.	June 8, 2007
Imidafenacin Uritos Tablets 0.1 mg	Kyorin Pharmaceutical Co., Ltd.	June 11, 2007
Imidafenacin Staybla Tablets 0.1mg	Ono Pharmaceutical Co., Ltd.	June 11, 2007
Ezetimibe Zetia Tablets 10 mg	Schering-Plough K.K.	June 11, 2007
Bevacizumab (Genetical recombination) Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL	Chugai Pharmaceutical Co., Ltd.	June 11, 2007
Celecoxib Celecox Tablets 100 mg and 200 mg	Astellas Pharma Inc.	June 12, 2007
Sodium Risedronate Hydrate Actonel Tab. 17.5 mg	Ajinomoto Co., Inc.	June 15, 2007
Sodium Risedronate Hydrate Benet Tablets 17.5 mg	Takeda Pharmaceutical Company Limited	June 15, 2007
Monobasic Sodium Phosphate Monohydrate/Dibasic Sodium Phosphate Anhydrous Visiclear Tablets	Zeria Pharmaceutical Co., Ltd.	June 15, 2007
Amiodarone Hydrochloride Ancaron Injection 150	Sanofi-Aventis K.K.	June 22, 2007
Carteolol Hydrochloride Mikelan LA Ophthalmic Solution 1% and 2%	Otsuka Pharmaceutical Co., Ltd.	July 3, 2007
Darbepoetin Alfa (Genetical recombination) Nesp Injection Syringe 10 μg syringe, 15 μg syringe, 20 μg syringe, 30 μg syringe, 40 μg syringe, 60 μg syringe, and 120 μg syringe	Kirin Pharma Company, Limited	July 9, 2007

Fludarabine Phosphate Fludara Tab. 10 mg	Bayer Yakuhin, Ltd.	July 12, 2007
Estradiol l'estrogel 0.06%	Shiseido Co.,Ltd.	August 9, 2007
Tadalafil Cialis Tablets 5 mg, 10 mg, and 20 mg	Eli Lilly Japan K.K.	September 12, 2007
Topiramate Topina Tablets 50 mg and 100 mg	Kyowa Hakko Kogyo Co., Ltd.	September 26, 2007
Montelukast Sodium Kipres Fine Granules 4 mg	Kyorin Pharmaceutical Co., Ltd.	October 2, 2007
Montelukast Sodium Singulair Fine Granules 4 mg	Banyu Pharmaceutical Co., Ltd.	October 2, 2007
Rocuronium Bromide Eslax Intravenous 25 mg/2.5 mL and 50 mg/5.0 mL	Nippon Organon K.K.	October 2, 2007
Garenoxacin Mesilate Hydrate Geninax Tablets 200 mg	Toyama Chemical Co., Ltd.	October 5, 2007
Idursulfase (Genetical recombination) Elaprase Solution for Intravenous Drip 6 mg	Genzyme Japan K.K.	October 17, 2007
Pilocarpine Hydrochloride Salagen Tab. 5 mg*1	Kissei Pharmaceutical Co., Ltd.	October 19, 2007
Nicorandil Sigmart Injection 2 mg, 12 mg, and 48 mg*2	Chugai Pharmaceutical Co., Ltd.	October 19, 2007
Clopidogrel Sulfate Plavix Tablets 25 mg and 75 mg*3	Sanofi-Aventis K.K.	October 19, 2007
Loratadine Claritin Tablets 10 mg, Claritin RediTab Tablets 10 mg*4	Schering-Plough K.K.	October 19, 2007
Travoprost Travatanz Ophthalmic Solution 0.004%	Alcon Japan Ltd.	October 25, 2007
Strontium Chloride (^{89}Sr) Metastron Injectable	Nihon Medi-Physics Co., Ltd.	October 31, 2007

*1: An additional indication for "the treatment of symptoms of dry mouth in patients with Sjogren's syndrome"

*2: An additional indication for "cardiac failure acute (including acute exacerbation of cardiac failure chronic)"

*3: An additional indication for "acute coronary syndrome (unstable angina pectoris, non ST segment elevation myocardial infarction) to which percutaneous coronary intervention (PCI) is being planned"

*4: Additional administration for "pediatrics"