Pharmaceuticals and Medical Devices Safety Information

No. 226 July 2006

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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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Pharmaceuticals and Medical Devices Safety Information

No. 226 July 2006

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

[Outline of Information]

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

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

Effects on implantable medical devices (cardiac pacemakers and cardioverter defibrillators) by new system mobile phone terminals

With regard to effects on implantable cardiac pacemakers and implantable cardioverter defibrillators (ICDs) (hereinafter referred to as "implantable medical devices") by mobile phone terminals etc., awareness was promoted in Pharmaceuticals and Medical Devices Safety Information No. 136 (March 1996 edition), No. 137 (May 1996 edition), No. 143 (June 1997 edition), No. 155 (June 1999 edition), No. 173 (January 2002 edition), No. 179 (July 2002 edition), No. 190 (June 2003 edition), No. 203 (July 2004 edition), and No. 216 (August 2005 edition).

Ministry of Internal Affairs and Communications (MIC) has been implementing studies relating to the effects of electromagnetic waves on medical devices since FY2000. In FY2005, "Guidelines for Preventing the Effects of Electromagnetic Waves From Various Types of Equipment on Implantable Medical Equipment" (established August 2005, hereinafter referred to as "Guidelines") was established based on the results of past studies.

Recently, MIC conducted a study on the effects on implantable medical devices from electromagnetic waves emitted from mobile phone terminals of a system that was newly implemented (800 MHz band W-CDMA system, hereinafter referred to as "new system mobile phone terminals"). As a result, it was publicized on May 30 of this year that it is appropriate to apply the current guidelines stating that "mobile phone terminals should be separated from the implant site of cardiac pacemakers by a distance of more than approximately 22 cm and more" even for mobile devices that were investigated in this study. In this issue, the contents of the study that was implemented by MIC recently are introduced.

With regard to the results of this study by MIC and the revised Guidelines based on this survey, please refer to [http://www.soumu.go.jp/s-news/2006/060530_1.html] (in Japanese), as well.

1. Contents of the recent study conducted by MIC

With regard to the effects of electromagnetic waves emitted from typical models of mobile phone terminals used in mobile telephone services of the 800 MHz band W-CDMA system recently put into practical use on typical models of implantable medical devices that are currently used, a study was conducted by establishing experimental conditions where these effects are thought to be the largest.

(1) Mobile phone terminals

With the cooperation of mobile telephone companies, a study was conducted on the following mobile phone terminal.

- New system mobile phone terminal (800 MHz band W-CDMA system): 1 model (note)

(note): For the mobile phone terminal subject to the study, a model with the highest radiation intensity of electromagnetic waves was selected from among the models that could be obtained while the study was being conducted.

(2) Implantable medical devices

With the cooperation of the Pacemaker Committee, a study was conducted on the following implantable medical devices.

- Implantable cardiac pacemakers: 30 models
- ICDs: 9 models

(3) Overview of study results

① With regard to implantable cardiac pacemakers, an effect to the pacing function(*1) was confirmed. This effect can be reduced and the pacemakers can be restored to their appropriate pacing functions if the mobile phone terminal is moved away. The distance at which this effect was confirmed when the mobile phone terminal was in a position the furthest away from the pacemakers (maximum interference distance) was 3 cm.

② With regard to ICDs, an effect on either the pacemaker function(*2) or defibrillation function(*3) could not be confirmed.

(Note): In this study, testing was performed under strict conditions, such as by setting the transmission output of the mobile phone terminal to the maximum, so that the effects on implantable medical devices would be the largest. Consequently, it is not appropriate to compare between the study condition (ex. including the largest distance away at which the effect was confirmed) and the normal condition, such as by setting to the regular transmission output of the mobile phone terminal.

<Reference Information>

*1: Effect on pacing function: The following conditions occur due to effects from external electromagnetic waves.
   a. In a state where a cardiac pacemaker, etc. is generating a pacing pulse in an intended pacing rate, a condition where the pacing pulse is inhibited due to the effects of external electromagnetic waves, or a condition where a change from the intended rate has occurred.
   b. In a state where the pacing pulse of a cardiac pacemaker, etc. is suppressed, a condition where a pacing pulse is generated due to effects from external electromagnetic waves.

*2: Pacemaker function of ICDs: ICDs normally include function as an implantable cardiac pacemaker, “pacemaker function” refers to this pacemaker function.

*3: Cardioverter defibrillation function of ICDs: Refers to the function of ICDs for providing a strong electric shock to stop ventricular fibrillation (a type of lethal arrhythmia, event where the heart causes sudden convulsions) detected by ICDs.

2. Precautions regarding implantable medical devices

Upon conducting this study, the maximum interference distance with regard to effects on implantable medical devices by new system mobile phone terminals was found to be 3 cm. At the same time, in the “Guidelines relating to the use of mobile phone terminals to prevent implantable medical devices from effects of electromagnetic waves” (*1), it is stipulated that mobile phone terminals should be “placed at least approximately 22 cm away” from the medical devices.

Consequently, since it is considered that effects on implantable medical devices by mobile phone terminals can be prevented by continuing to adhere to “placed at least approximately 22 cm away” that is given in the current guidelines, it is request that patients continue to be instructed to adhere to the current guideline, and that family members, etc. also be instructed to do so if the patient is a child, etc.

*1: This translation was based on the description of PMDSI in Japanese.

2

Important Safety Information

This section presents contents of revisions, reference materials, and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No.225).

1 Atorvastatin Calcium Hydrate

Brand Name (name of company)	Lipitor Tablets 5 mg and 10 mg (Astellas Pharma Inc.)
Therapeutic Category	Hyperlipidaemia agents
Indications	Hypercholesterolaemia Familial hypercholesterolaemia

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

[Important Precautions]

Hepatitis such as hepatitis fulminant may occur. Patients should be instructed to discontinue administration of this drug and contact a physician etc. if symptoms such as nausea, vomiting and malaise etc. occur.
During administration, liver function tests should be conducted at least once within 12 weeks after initiating administration or after increasing the dosage, and periodically afterwards (once every 6 months etc.).

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis fulminant, hepatitis, hepatic function disorder, jaundice: Patient should be carefully monitored through periodic testing etc. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to April 26, 2006) (events for which a causality to the drug could not be denied)
• Hepatitis fulminant, hepatitis: 12 cases (of which 4 had a fatal case)
The number of patients treated with Atorvastatin for a year estimated by MAH (Marketing Authorisation Holder): approximately 2.1 million (FY 2005)
Marketed in Japan in: May 2000

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 50s	Hyperlipidaemia (reflux oesophagitis, ovarian failure, gastric ulcer, insomnia, climacteric disturbance)	10 mg 77 days	**Hepatitis fulminant** 3 days before administration: Low back pain developed. After 3 or 4 times of oral administrations of OTC analgesic drugs, epigastralgia, queasy and vomiting developed. The patient was drinking fluids, but vomited immediately and did not intake any food at all. The patient seemed to have been taking OTC drugs (cold medicine) often, but details are unknown. History of blood transfusions: unknown.	Company report

				1 day before administration: Since the symptoms persisted, the patient made an outpatient visit to hospital A. She was hospitalized after undergoing drip infusion. The patient was diagnosed with reflux oesophagitis, gastric ulcer, insomnia, hyperlipidaemia, and climacteric disturbance, and was prescribed oral medicines. On day 1 of administration: Administration of this drug, lansoprazole, zolpidem tartrate, quazepam, mosapride citrate, and domperidone was initiated. On day 2 of administration: Administration of conjugated estrogens and medroxyprogesterone acetate was initiated. On day 4 of administration: Symptoms for reflux oesophagitis (queasy) improved. The patient was discharged from the hospital. On day 22 of administration: Administration of mosapride citrate and domperidone was discontinued. On day 64 of administration: Administration of zolpidem tartrate and quazepam was discontinued. On day 75 of administration: The patient laid her work aside and went home due to physical deconditioning. On day 77 of administration (day of discontinuation): Administration of this drug and lansoprazole discontinued. 3 days after discontinuation: The patient was sleeping or eating, and continued vomiting. Administration of conjugated estrogens and medroxyprogesterone acetate was discontinued. 4 days after discontinuation: Around noon, the patient was emergently sent to hospital A due to loss of consciousness since the morning. Due to advanced liver disorder and consciousness disturbed (hepatic encephalopathy: stage IV, JCS: 300), the patient was sent to emergency center of hospital B. Immediately after transportation, the patient was fitted with tracheal intubation and respirator. Since she also had renal disorder, CHDF (continuous hemodiafiltration) was initiated. Administration of fresh frozen human plasma and plasma exchange were initiated. Afterwards, hypothermia (unmeasurable) developed, and blood pressure was 88/48 mmHg, pulse was 86 pulses/minute, JCS was 30 to 100, jaundice was (−) and coloring yellow was (−). Hypoglycaemic with a blood sugar of 38 mg/dL was also indicated, and diagnosed as having hepatic encephalopathy of stage III and diagnosed with hepatitis fulminant. In the nighttime, plasma exchange (40 units of fresh frozen human plasma) was performed. Afterwards, CHDF (300 mL/h of dialysate, 700 mL/h of fluid replacement and 1000 mL/h of physiological saline) was initiated as artificial hepatic assist treatment.	

				Methylprednisolone sodium succinate at 1 g/day was administered as immunosuppressive treatment. No abnormalities were found in chest/abdominal X rays. Based on abdominal CT, intrahepatic ductal dilatation was (–), dilatation of the common bile duct was (–), ascites were (–) and there was atrophy in the hepatic left lobe. Based on an echo, the surface of the liver was smooth, marginal dull, intrahepatic mass was (–), and ascites were (–). 5 days after discontinuation: In the morning, hepatic encephalopathy was worsened to stage V. Although they attempted to perform a DLST, the lymphocyte count was low and could not be measured. Consideration was given to a liver transplant but was abandoned due to the decision that the patient would not be able to tolerate a transplant due to vitals being unfavorable. In the night, blood pressure was decreased to the 60 mmHg range. 6 days after discontinuation: Blood pressure and pulse continued to decrease. The patient died before dawn. Hepatic necropsy: Necrosis of band-like necrosis hepatocellular in area around central venous was confirmed. It was accompanied by haemorrhage. Small amount of eosinophils and infiltration of neutrophil are confirmed in portal region, but significant lymphocytic infiltration and cholangiole reactions were obscure. Though inflammatory reactions were scarce, necrosis of necrosis hepatocellular was conspicuous, and eosinophilic infiltration was confirmed. (cause of death: hepatitis fulminant)	
	Concomitant medications: zolpidem tartrate, lansoprazole, medroxyprogesterone acetate, conjugated estrogens, quazepam, mosapride citrate, domperidone				

Clinical Laboratory Values

	On day 1 of administration	4 days after discontinuation	5 days after discontinuation
AST (GOT) (IU/L)	19	4950	5005
ALT (GPT) (IU/L)	13	1935	1469
Al-P (IU/L)	401	566	422
γ-GTP (IU/L)	80	409	263
LDH (IU/L)	192	5971	7926
Total bilirubin (mg/dL)	0.4	2.5	3.9
Prothrombin activity (%)	--	30.0	51.1
Blood ammonia (μg/dL)	--	687	234
HAV (–), HBV (–), HCV (–), CMV (–), EBV infected, antinuclear antibody (–)			

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

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 50s	Hypercholesterolaemia (essential hypertension, angina pectoris, and suspected diabetes mellitus)	5 mg 55 days	**Drug-induced hepatitis** 2 days before administration: The patient complained of non-rotatory vertigo from early morning 2 days before, and made a hospital visit. Blood pressure was 180/100 mmHg. Findings of a decrease in ST were confirmed in an electrocardiogram. Heart rate was 95 beats/minute, total cholesterol was 242 mg/dL in blood test. Triglyceride was 120 mg/dL and HDL-cholesterol was 60 mg/dL. Glucose (2+) was confirmed in urine analysis. On day 1 of administration: Administration of this drug, valsartan, trapidil, and kallidinogenase was initiated. On day 4 of administration: 75 g glucose tolerance test was performed. As a result, 87 mg/dL before tolerance, 167 mg/dL after 30 minutes, 135 mg/dL after 60 minutes, 115 mg/dL after 120 minutes. With regard to diabetes mellitus, only dietary instructions were given. On day 55 of administration (day of discontinuation): Abnormal value was confirmed in liver function test, administration of this drug, valsartan, trapidil, and kallidinogenase was discontinued. 1 day after discontinuation: Drip infusion of 500 mL of 5% glucose and 40 mL of glycyrrhizin/glycine/cysteine was initiated (for 10 days). 2 days after discontinuation: Based on negative hepatitis viral markers and normal antinuclear antibody, the patient was diagnosed with drug-induced hepatitis. 12 days after discontinuation: Intravenous injection of 40 mL of glycyrrhizin/glycine/cysteine was initiated (for 12 days). 22 days after discontinuation: The symptoms were improved.	Company report
	Concomitant medications: valsartan, trapidil, kallidinogenase				

Clinical Laboratory Values

	On day 55 of administration (day of discontinuation)	2 days after discontinuation	5 days after discontinuation	12 days after discontinuation	17 days after discontinuation	22 days after discontinuation
AST (GOT) (IU/L)	1551	1049	379	81	48	38
ALT (GPT) (IU/L)	2560	2300	1200	268	103	52
Al-P (IU/L)	530	797	784	475	332	278
γ-GTP (IU/L)	244	270	519	362	255	199
LDH (IU/L)	--	950	394	273	259	253
Total bilirubin (mg/dL)	1.3	1.7	1.4	1.2	1.5	1.4
Hepatitis virus (–), antinuclear antibody normal						

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

2 Goshajinkigan

Brand Name (name of company)	TSUMURA Goshajinkigan Extract Granules for Ethical Use (Tsumura & Co.)
Therapeutic Category	Kampo medicines
Indications	Following symptoms with decreased urine volume, polyuria, occasional dry mouth, fatiguability and feeling of cold in the extremities: Leg pain, low back pain, numbness, blurred vision in old patients, pruritus, dysuria, frequent urination and oedema

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

[Adverse Reactions (clinically significant adverse reactions)]	**Interstitial pneumonia:** If pyrexia, cough, dyspnoea, abnormal chest sound (crepitations), etc. occur, administration should be discontinued. Immediately perform a chest X-ray and undergo examinations, and appropriate measures such as administration of an adrenocortical hormone preparation should be taken. Patient should be instructed to discontinue administration and immediately contact a physician if pyrexia, cough, and dyspnoea, etc. occur.
<Reference Information>	The number of reported adverse reaction cases in about the last 3 years (April 1, 2003 to April 11, 2006) (events for which a causality to the drug could not be denied) • Interstitial pneumonia: 1 case (no fatal case) The number of patients treated with Goshajinkigan for a year estimated by MAH: approximately 170000 (FY2005) Marketed in Japan in: 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 70s	Pain in right knee (hyperthyroidism, interstitial pneumonia, pain in right knee)	7.5 g 119 days	**Interstitial pneumonia** Approx. 16 years before administration: Due to aortic stenosis, the patient was visiting this department regularly. Approx. 3 years before administration: Pulmonary fibrosis was confirmed, but it was localized to part of the right lower lobe. On day 1 of administration: Administration of this drug was started for pain in right knee. On day 110 of administration: Body temperature was increased to 37.4°C, and dry cough and dyspnoea of HJ IV to V on exertion developed. On day 119 of administration (day of discontinuation): The patient received an outpatient consultation from this department. Since extensive ground-glass opacity had newly developed mainly around the right upper and lower lung fields, the patient underwent emergency hospitalization on the same day. Since atypical pneumonia could not be denied based on chest findings, CRP increased, slight fever etc., clarithromycin was administrated. Administration of this drug was discontinued and observing clinical course, the symptoms improved with rest. 42 days after discontinuation: The patient was discharged from the hospital. She was undergoing monitoring of clinical course as an outpatient. 50 days after discontinuation: Worsening of symptoms was not confirmed.	Company report
	Concomitant medications: thiamazole, diltiazem hydrochloride, etizolam				

Clinical Laboratory Values

	Before administration	On day 55 of administration	On day 119 of administration (day of discontinuation)	29 days after discontinuation	50 days after discontinuation
WBC (/mm^3)	4100	4000	5800	4400	4700
Eosinophils (%)	0.3	0.2	8.0	2.4	0.7
LDH (IU/L)	193	209	243	208	--

WBC: White Blood Cell LDH: Lactate Dehydrogenase

Blood gases

	On day 119 of administration (day of discontinuation)	9 days after discontinuation	29 days after discontinuation
pH	7.432	7.436	7.405
PaO_2 (torr)	70.1	69.2	84.6
$PaCO_2$ (torr)	37.9	38.2	40.1

PaO_2: Partial Pressure Arterial Oxygen $PaCO_2$: Partial Pressure of Carbon Dioxide in Artery

Immune serum test

	On day 119 of administration (day of discontinuation)	1 day after discontinuation
RA test	Negative	--
Antinuclear antibody	--	Positive
Complement CH50	--	49

DLST (S.I.)

	10 days after discontinuation
This drug	523%

3

Revision of PRECAUTIONS (No. 177)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No.225) (excluding those presented in "2. Important Safety Information" of this Bulletin), together with reference materials.

1 <Psychotropics> Chlorpromazine Hydrochloride/Promethazine Hydrochloride/Phenobarbital

[Brand Name] Vegetamin Tablets-A, Vegetamin Tablets-B (Shionogi & Co., Ltd.)

[Contraindications] Infants under 2 years of age

[Use in Children] This drug should not be used in infants under 2 years of age. [It has been reported that in foreign countries, administration of promethazine drugs to infants under 2 years of age has resulted in life-threatening respiratory depression.]

<Reference Information> Company report

2 <Psychotropics> Paroxetine Hydrochloride Hydrate

[Brand Name] Paxil Tablets 10 mg and 20 mg (GlaxoSmithKline K.K.)

[Important Precautions] Since it has been reported that young adults, especially those with major depressive disorder (MDD), may be at increased risk for suicidal behaviour (completed suicide and suicide attempt) during treatment with this drug.careful monitoring should be given in such patients.

[Other Precautions] As a results of an analysis of the placebo-controlled clinical trials of this drug in adult patients with psychiatric disorders conducted overseas, although the study showed a higher frequency of suicidal behaviour(completed suicide and suicide attempt) in patients aged 18-24 years) treated with this drug compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In patients with MDD, there was a statistically significant increase in the frequency of suicidal attempts in patients treated with this drug compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]; all of the events were suicide attempts). The majority of these attempts for this drug were in patients aged 18-30 years..

<Reference Information> Company report

3 <Psychotropics> Hydroxyzine Hydrochloride, Hydroxyzine Pamoate

[Brand Name] Atarax, Atarax Tablets 25 mg, Atarax-P Parenteral Solution (Pfizer Japan Inc.) and others
Atarax-P Powder 10%, Atarax-P, Atarax-P Syrup, Atarax-P Dry Syrup (Pfizer Japan Inc.) and others

[Contraindications]

Patients with a history of hypersensitivity to ingredients of this drug, cetirizine, piperazine derivative, aminophylline, or ethylenediamine
Patients with porphyria
Pregnant women or women who may be pregnant

[Use in Pregnant, Parturient and Nursing Women] This drug should not be used in pregnant women or women who may be pregnant [It has been reported that upon administering this drug to women in the early stage of pregnancy (approximately 3 months), the women gave birth to babies with birth defects such as cleft palates. In addition, it has also been reported that due to administration of this drug during pregnancy, psychoneurotic symptoms such as somnolence neonatal, hypotonia neonatal, withdrawal symptoms, extrapyramidal disorder, clonic movements, and central nervous system depression, and neonatal hypoxia were observed in neonates.]
This drug should not be administered to nursing mothers. [Although excretion of this drug in breast milk has not been established, it has been reported that central nervous system depression and hypotonicity have developed in neonates while nursing.]

<Reference Information> Company report

4 <Common cold drugs> Salicylamide/Acetaminophen/Anhydrous Caffeine/Promethazine Methylenedisalicylate

[Brand Name] PL Granules, PL Granules for Children (Shionogi & Co., Ltd.) and others

[Contraindications]

Infants under 2 years of age

[Use in Children] This drug should not be used in infants under 2 years of age. [It has been reported that in foreign countries, administration of promethazine drugs to infants under 2 years of age has resulted in life-threatening respiratory depression.]

<Reference Information> Company report

5 <Ophthalmic agents> Latanoprost

[Brand Name] Xalatan Eye Drops (Pfizer Japan Inc.)

[Important Precautions] Temporary vision blurred may occur after ocular instillation of this drug. Patients should be advised to refrain from engaging in operating machines or driving a car etc. until symptoms recover.

<Reference Information> Company report

6 <Antihypertensives> Valsartan

[Brand Name] Diovan Tablets 20 mg, 40 mg, 80 mg, and 160 mg (Novartis Pharma K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, white blood cell decreased, platelets decreased:
Agranulocytosis, white blood cell decreased, and platelets decreased may occur. Patient should be carefully monitored and if any abnormalities are observed, appropriate measures should be immediately taken.

<Reference Information> Company report

7 <Antihistamines> Promethazine Hydrochloride, Promethazine Hibenzate, Promethazine Methylenedisalicylate

[Brand Name] Hiberna Sugar-coated Tablets 5 mg and 25 mg, Hiberna Injection (Mitsubishi Pharma Corporation), Pyrethia Tablets (Shionogi & Co., Ltd.) and others
Hiberna Powder 10% (Mitsubishi Pharma Corporation)
Pyrethia Fine Granules (Shionogi & Co., Ltd.)

[Contraindications] Infants under 2 years of age

[Use in Children] This drug should not be used in infants under 2 years of age. [It has been reported that in foreign countries, administration to infants under 2 years of age has resulted in life-threatening respiratory depression.]

<Reference Information> Company report

8 <Biological preparations-Miscellaneous> Bacillus Calmette-guerin (BCG)/Japan strain

[Brand Name] Immunobladder Intravesical 40 mg and 80 mg (Japan BCG Laboratory)

[Adverse Reactions (clinically significant adverse reactions)]

BCG infection: This drug is a live bacterial preparation, and may cause disseminated BCG infection, local BCG infection and ectopic BCG infection. In addition, sepsis, hepatitis, cerebrospinal meningitis, cystitis, pyelonephritis, nephritis, prostatitis, epididymitis, aneurysm, etc. may occur. Discontinue administration and take appropriate measures in such cases, and conduct combination therapy with chemotherapeutics-tuberculosis preparations such as isoniazid, rifampicin and ethambutol. BCG is not susceptible to pyrazinamide.

Disseminated BCG infection: In clinical trials of this drug, cases of death thought to be resulting from disseminated BCG infections associated with administration of BCG after traumatic injury from catheter insertion etc. were confirmed. Disseminated BCG infection is suggested by influenza-like febrile symptoms that persist for 48 hours and more, pyrexia of 39°C and higher, generalized symptoms that grow intense from repeated dose, or continuation of liver function test abnormalities.

Local BCG infection: Continued BCG infection in the ureter, renal pelvis, kidney, prostate, epididymis, etc. of the bladder and lumen where this drug was locally administered has been reported.

Ectopic BCG infection: Ectopic BCG infection in aneurysms etc. has been reported.

Renal failure: Serious renal disorders such as renal failure etc. may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures, such as discontinuing treatment should be taken.

<Reference Information> Company report

9 Over the counter drugs
Goshajinkigan

[Brand Name] Kanebo Goshajinkigan Extract Tablets (Kanebo, Ltd.) and others

[Consultation] In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.

If the following symptoms are observed after taking this drug

In rare instances, the following serious symptoms may occur. Visit a physician immediately in such cases.

Interstitial pneumonia: Shortness of breath, dyspnoea, and pyrexia accompanying cough may occur.

<Reference Information> Company report

4

List of products subject to Early Post-marketing Phase Vigilance

(As of July1, 2006)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Miglitol Seibule Tab. 25 mg, 50 mg, and 75 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	January 11, 2006
Potassium Clavulanate/Amoxicillin Clavamox Dry Syrup for Pediatric	GlaxoSmithKline K.K.	January 17, 2006
Paroxetine Hydrochloride Hydrate Paxil Tablets 10 mg and 20 mg[*1]	GlaxoSmithKline K.K.	January 23, 2006
Ciclosporin Papilock Mini Ophthalmic Solution 0.1%	Santen Pharmaceutical Co., Ltd.	January 23, 2006
Placental Gonadotrophin Profasi Injection 5000[*2]	Serono Japan Co., Ltd.	January 30, 2006
Zanamivir Hydrate Relenza[*3]	GlaxoSmithKline K.K.	February 17, 2006
Baclofen Intrathecal Gabalon 0.005%, 0.05%, and 0.2%	Daiichi Pharmaceutical Co., Ltd.	April 1, 2006
Interferon Beta Feron[*4]	Toray Industries, Inc.	April 20, 2006
Epoetin Beta (Genetical recombination) Epogin Injection Ampoule 750, 1500, and 3000, Epogin Injection Syringe 750, 1500, and 3000[*5]	Chugai Pharmaceutical Co., Ltd.	April 20, 2006
Somatropin (Genetical recombination) Humatrope C 6 mg and 12 mg[*6]	Eli Lilly Japan K.K.	April 20, 2006
Zoledronic Acid Hydrate Zometa Injection 4 mg[*7]	Novartis Pharma K.K.	April 20, 2006
Micafungin Sodium Funguard 50 mg and 75 mg for Infusion[*8]	Astellas Pharma Inc.	April 20, 2006
Linezolid Zyvox Tablets 600 mg, Zyvox Injection 600 mg[*9]	Pfizer Japan Inc.	April 20, 2006
Tosufloxacin Tosilate Tosuflo Ophthalmic Solution 0.3%	Nidek Co., Ltd.	April 28, 2006
Clopidogrel Sulfate Plavix Tablets 25 mg and 75 mg	Sanofi-Aventis K.K.	May 8, 2006
Silodosin Urief Cap. 2 mg and 4 mg	Kissei Pharmaceutical Co., Ltd.	May 11, 2006
Tosufloxacin Tosilate Ozex Ophthalmic Solution 0.3%	Toyama Chemical Co., Ltd.	May 11, 2006
Follitropin Alfa (Genetical recombination) Gonalef for S.C. Injection 75 and 150	Serono Japan Co., Ltd.	May 11, 2006

Letrozole Femara Tablets 2.5 mg	Novartis Pharma K.K.	May 11, 2006
Loxoprofen Sodium Loxonin PAP 100 mg	Lead Chemical Co., Ltd.	May 23, 2006
Aripiprazole Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%	Otsuka Pharmaceutical Co., Ltd.	June 8, 2006
Solifenacin Succinate Vesicare Tablets 2.5 mg and 5 mg	Astellas Pharma Inc.	June 8, 2006
Tolterodine Tartrate Detrusitol Capsules 2 mg and 4 mg	Pfizer Japan Inc.	June 8, 2006
Amphotericin B AmBisome for Intravenous Infusion 50 mg	Dainippon Sumitomo Pharma Co., Ltd.	June 20, 2006
Magnesium Sulfate/Glucose Magsent Injection 100 mL	TOA Pharmaceuticals Co., Ltd.	June 20, 2006

Note) Subject to additional indication etc.

*1: An additional indication for “obsessive-compulsive disorder”

*2: An additional indication for “induction of spermatogenesis in hypogonadotropic male hypogonadism”

*3: An additional administration for “pediatrics”

*4: An additional indication for “the improvement of viremia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA level)”

*5: An additional indication for “anemia of prematurity”

*6: An additional indication for “adult growth hormone hyposecretion (severe cases only)”

*7: An additional indication for “bone lesions due to multiple myeloma and solid tumor metastases to bone”

*8: An additional administration for “pediatrics”

*9: Additional indications for “<Susceptible strains> methicillin-resistant Staphylococcus aureus (MRSA) sensitive to this drug <Indications> sepsis, deep skin infection, chronic pyoderma, secondary infection such as from traumatic injury/fever and surgical wound, and pneumonia”