Pharmaceuticals and Medical Devices Safety Information

No. 271 July 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 (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) 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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Pharmaceuticals and Medical Devices Safety Information
No. 271 July 2010

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

Outline of Information

No.	Subject	Measures	Outline of Information	Page
1	**Precautions in Handling of Bipolar Electrode U'sed along with Electrosurgical Device**		The bipolar electrode used along with the electrosurgical device must not be connected to an output terminal of the monopolar electrode with a 'Flying-lead' extension cord. Healthcare professionals have been repeatedly alerted via the package inserts. A case where unexpected burn occurred due to erroneously connecting the bipolar electrode via the 'Flying-lead' to the monopolar terminal has been reported, and similar medical accidents may occur at other medical institutions. In this section, precautions in handling of bipolar electrosurgical devices are presented.	4
2	**Olmesartan Medoxomil (and 1 other)**	*P* *C*	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 July 6, 2010.	8
3	**Phenytoin (and 5 others)**		Revision of Precautions (No. 218)	15
4	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of July 1, 2010.	18

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

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi," a Pharmaceuticals and Medical Devices Information E-mail Alert Service (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. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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 authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

1

Precautions in Handling of Bipolar Electrode Used along with Electrosurgical Device

1. Introduction

The bipolar electrode used along with the electrosurgical device has 2 types of extension cord: 'Fixed-plug' and 'Flying-lead'. (**Figure 1**)

The 'Flying-lead' cord can be erroneously connected to an output terminal of the monopolar electrode. (**Figure 2**)

In September 2004, the Ministry of Health, Labour and Welfare (MHLW) has commissioned product manufacturers of electrosurgical devices and bipolar electrodes to revise the package inserts to include cautions that state not to connect the 'Flying lead' extension cord to the monopolar terminal, and to provide relevant information to healthcare professionals..[1)]

Erroneously connecting the bipolar electrode via the 'Flying-lead' code to the monopolar terminal may cause unexpected burn. So far, 1 case has been reported during January 2005 to December 2009[2)], and similar medical accidents may occur at other medical institutions. Precautions for use of the bipolar electrode are provided below.

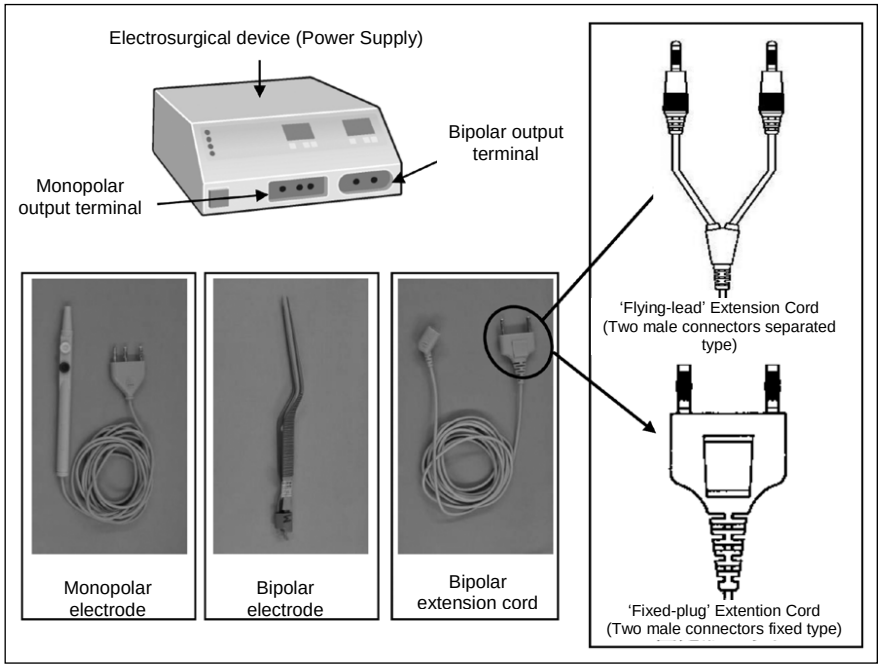


Figure 1. Structure of electrosurgical device and electrodes

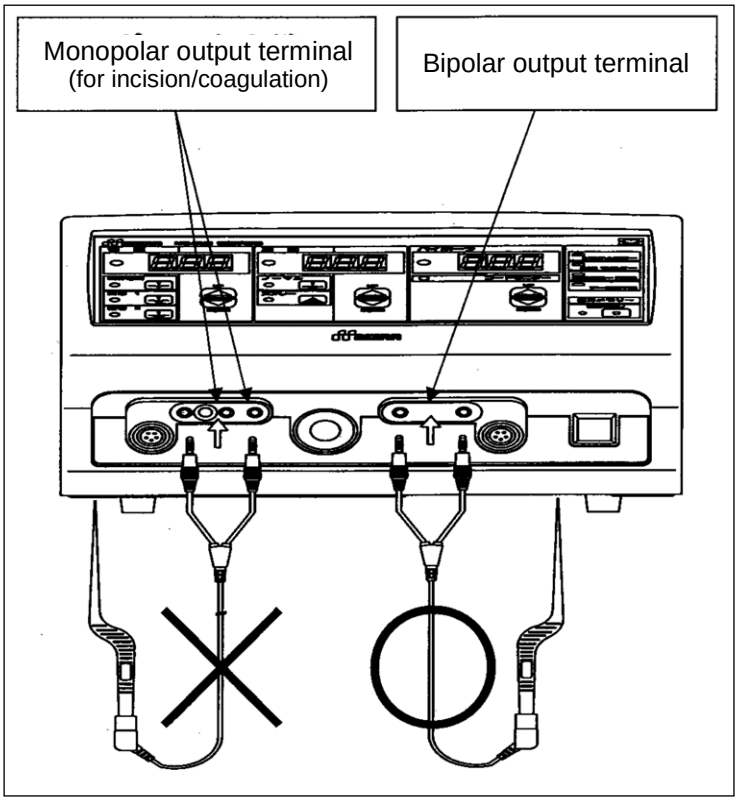


Figure 2. Image of erroneous connection
(Note: This illustration does not indicate the device which was actually used in the reported accident.)

2. Request to healthcare professionals

When handling the bipolar electrode used along with the electrosurgical device, please take note of the following precautions:

1. Use of 'Fixed-plug' extension cord is recommended when connecting the bipolar electrode to the electrosurgical device because a freely-connectable 'Flying-lead' extension cord may be erroneously connected to a monopolar output terminal.
2. Specifications of the 'Fixed-plug' extension cord (such as spacing between male connectors) may vary depending on the product. It is necessary to check whether the extension cord is connectable by reading the package insert and/or the instructions for use of "the electrosurgical device (power supply)" and/or "the 'Fixed-plug' bipolar extension cord".
3. In the case where the 'Flying-lead' bipolar extension cord has to be used until the 'Fixed-plug' bipolar extension cord suitable to each electrosurgical device is distributed, be sure to connect the 'Flying-lead' bipolar extension cord correctly to the bipolar output terminal.

The MHLW has required manufacturers of the bipolar electrodes used along with the electrosurgical devices to revise the package inserts of their products (**Figure 3**), and provide relevant information to healthcare professionals[3)]

In addition, the MHLW has also requested these manufacturers to discontinue the marketing of the 'Flying-lead' extension cords by the end of 2010.

3. An accident caused by erroneous connection of the bipolar extension cord

While preparing for a surgery, a surgeon handed cords for an electrosurgical device to a circulating nurse, the nurse hurriedly connected a bipolar extension cord to a monopolar output terminal. This erroneous connection left the electrode continuously conducting electricity. Not knowing this, the surgeon held the sigmoid colon with the electrode, which caused an unexpected burn. The patient was treated by suturing the serosa in the burned area.[2)]

4. Closing comments

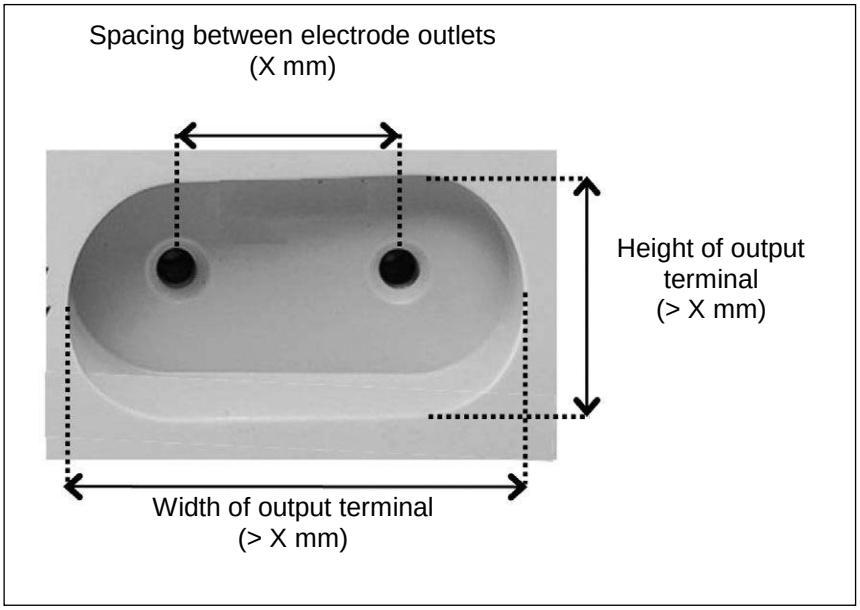
The PMDA released Medical Safety Information concerning handling of electrosurgical devices.[4)] Please use the information for safety management at your medical institution.

For details of this alert[3)] and the regulatory request to the manufacturers of the bipolar electrode used along with the electrosurgical device,[5)] please refer to the PMDA website.

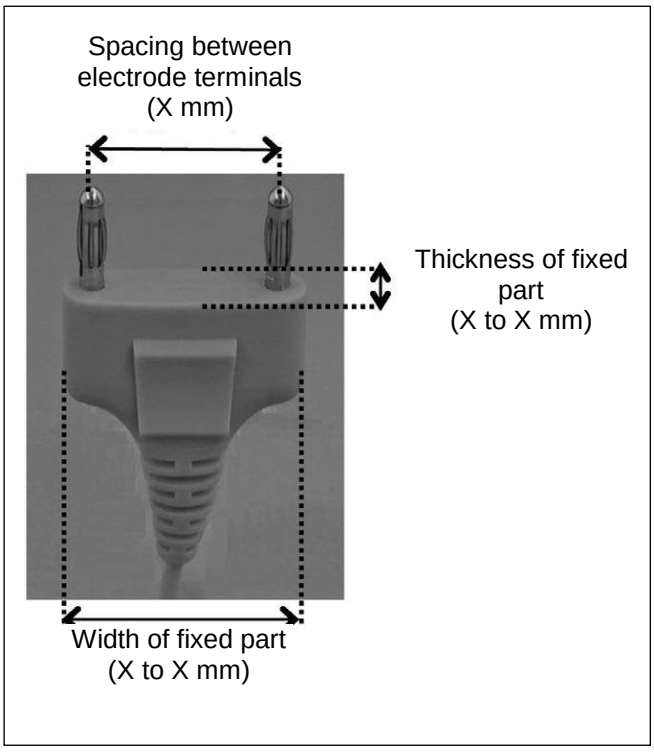
http://www.info.pmda.go.jp/iryoujiko/iryoujiko_index.html (only available in Japanese language)
http://www.info.pmda.go.jp/mdevices/md-tenken-2010.html (only available in Japanese language)
http://www.info.pmda.go.jp/anzen_pmda/iryo_anzen.html (only available in Japanese language)
http://www.pmda.go.jp/english/service/medical_info.html (in English)

<References> (including provisionally translated titles)

1) Joint PFSB/ELD Notification No. 0924006 and PFSB/SD Notification No. 0924004, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, the MHLW, dated September 24, 2004, "Self-inspections, etc. for handling of bipolar electrodes and electrosurgical devices" (only available in Japanese language)
2) Japan Council for Quality Health Care : "Project to collect medication error cases: the 17th report" page 130; June 2009 (only available in Japanese language)
3) Joint HPB/GAD Notification No. 0609-1 and PFSB/SD Notification No. 0609-1, by the Director of General Affairs Division, Health Policy Bureau and by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, the MHLW, dated June 9, 2010, "Handling of bipolar electrodes of electrosurgical devices (request for provision of information to users)" (only available in Japanese language)
4) Pharmaceuticals and Medical Devices Agency (PMDA) Medical Safety Information No. 14 to No. 16 "Precautions in Handling of Electric Scalpels (part 1 to 3)" (only available in Japanese language)
5) Joint PFSB/SD Notification No. 0609-3 and PFSB/ELD/OMDE Notification No. 0609-1, by the Director of Safety Division, Pharmaceutical and Food Safety Bureau and by the Director of Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the MHLW, dated June 9, 2010, "Self-inspections, etc. for handling of bipolar electrodes and electrosurgical devices" (only available in Japanese language)



Appearance of bipolar output terminal of electrosurgical device (power supply)



Appearance of fixed plug

Figure 3. Example of package insert description

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 July 6, 2010.

[Brand name]: Major product names are showed.

1 Olmesartan Medoxomil, Olmesartan Medoxomil/Azelnidipine, Telmisartan, Telimsartan/Hydrochlorothiazide, Valsartan, Valsartan/Amlodipine Besilate, Valsartan/Hydrochlorothiazide

Brand Name (name of company)	**Olmesartan Medoxomil** OLMETEC TABLETS 5 mg, 10 mg, 20 mg, 40 mg (Daiichi Sankyo Company, Limited) **Olmesartan Medoxomil/Azelnidipine** REZALTAS COMBINATION TABLETS LD, HD (Daiichi Sankyo Company, Limited) **Telmisartan** Micardis Tablets 20 mg, 40 mg, 80 mg (Nippon Boehringer Ingelheim Co., Ltd.) **Telmisartan/Hydrochlorothiazide** Micombi Combination Tablets AP, BP (Nippon Boehringer Ingelheim Co., Ltd) **Valsartan** DIOVAN Tablets 20 mg, 40 mg, 80 mg, 160 mg (Novartis Pharma K.K.) **Valsartan/Amlodipine Besilate** EXFORGE Combination Tablets (Novartis Pharma K.K.) **Valsartan/Hydrochlorothiazide** Co-DIO combination tablets MD, EX (Novartis Pharma K.K.)
Therapeutic Category	Antihypertensives
Indications	Hypertension

≪PRECAUTIONS (underlined parts are additions)≫

[Adverse Reactions (clinically significant adverse reactions)]

Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feeling of weakness, increased CK (CPK), increased blood myoglobin and increased urine myoglobin may occur. Patients should be carefully monitored and if such symptoms are observed, administration should be discontinued immediately and appropriate measures should be taken.

<Reference Information>

Olmesartan Medoxomil

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 May 27, 2010):

• Rhabdomyolysis: 1 case (no fatality)

The number of patients treated with this drug per year estimated by marketing authorization holder (MAH): approximately 1.81 million (for FY 2009)

Marketed in Japan in: May 2004 (Olmesartan Medoxomil)
April 2010 (Olmesartan Medoxomil/Azelnidipine)

Telmisartan

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 May 27, 2010):

• Rhabdomyolysis: 3 cases (no fatalities)

The number of patients treated with this drug per year estimated by MAH: approximately 1.9 million (for FY 2009)

Marketed in Japan in: January 2005 (Telmisartan/Hydrochlorothiazide, Micardis Tablets)

[December 2002 to March 2006 (Telmisartan / Hydrochlorothiazide, Micardis Capsules)]

June 2009 (Telmisartan/Hydrochlorothiazide)

Valsartan

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 May 27, 2010):

• Rhabdomyolysis: 4 cases (no fatalities)

The number of patients treated with this drug per year estimated by MAH: approximately 4.1 million (for FY 2009)

Marketed in Japan in: November 2000 (Valsartan)

March 2009 (Valsartan/Hydrochlorothiazide)

April 2010 (Valsartan/Amlodipine Besilate)

Case Summary
<Olmesartan Medoxomil>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 40s	Hypertension (Diabetes mellitus, hepatic steatosis, hyperlipidaemia)	20mg for 28 days	**Rhabdomyolysis** Day 1 of administration: The patient had taken amlodipine besilate and candesartan cilexetil, but medication was switched to nifedipine and olmesartan medoxomil 20 mg/day. Administration of ursodeoxycholic acid was started at the same time because of changes in liver function test values. The patient underwent muscle training at irregular intervals. Day 14 of administration: AST (GOT) 83 IU/L, ALT (GPT) 81 IU/L, CK (CPK) 216 IU/L. Day 24 of administration: The patient started muscle training. (20 sit-ups × 2 to 3 sets and 20 push-ups × 2 to 3 sets, twice every 3 days; The patient has usually done 20 sit-ups.) Day 28 of administration (day of discontinuation): CK (CPK) increased markedly. Administration of olmesartan medoxomil was discontinued and parenteral nutrition was given. Blood and urinary myoglobin increased, and the patient was diagnosed with rhabdomyolysis. AST (GOT) 177 IU/L, ALT (GPT) 105 IU/L, CK (CPK) 7352 IU/L, blood myoglobin 533.1 ng/mL, urine myoglobin 193.4 ng/mL 3 days after discontinuation: CK (CPK) decreased to around 1700 IU/L. 4 days after discontinuation: Pyresia (around 38°C) associated with a common cold was noted. 5 days after administration: The patient consulted another hospital and received parenteral nutrition. CK (CPK) was

				around 300 IU/L. 14 days after discontinuation: CK (CPK) returned to normal, and the patient recovered. AST (GOT) 72 IU/L, ALT (GPT) 116 IU/L, CK (CPK) 149 IU/L.
	Concomitant medications: nifedipine, ursodeoxycholic acid, lansoprazole			

Clinical Laboratory Values

	1 day before administration:	Day 14 of administration	Day 28 of administration (day of discontinuation)	14 days after discontinuation
AST (GOT) (IU/L)	114	83	177	72
ALT (GPT) (IU/L)	142	81	105	116
Al-P (IU/L)	182	162	198	178
CK (CPK) (IU/L)	178	216	7352	149
γ-GTP (IU/L)	333	277	359	271
BUN (mg/dL)	10.2	13.7	14.6	15.0
Creatinine (mg/dL)	0.81	0.79	0.62	0.84
CRP (mg/dL)	0.09	0.17	0.15	0.19
WBC (/mm^3)	3960	3810	3940	4900
RBC (× 10^4/mm^3)	493	459	479	503
Hemoglobin (g/dL)	15.7	14.6	15.4	16.1
Blood myoglobin (ng/mL)	-	-	533.1	-
Urine myoglobin (ng/mL)	-	-	193.4	-

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), Al-P: Alkaline phosphatase, CK: Creatine kinase, γ-GTP: gamma-glutamyl transpeptidase, BUN: Blood urea nitrogen, CRP: C-reactive protein, WBC: White blood cell count, RBC: Red blood cell count

<Valsartan>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Hypertension (Aortic dissection)	80 mg for 4 days ↓ 160mg for 5 days	**Rhabdomyolysis** Day 1 of administration: The patient was transferred by ambulance in the morning for chest and back pain that had occurred while he was playing golf. He was admitted to the hospital. Administration of this drug (valsartan) 80 mg/day was started. Day 4 of administration: The patient had slight and tolerable pain in lower limbs. Next day the dose of valsartan was increased to 160 mg/day. Day 6 of administration: Pain of lower extremities was aggravated. CK (CPK) 321 IU/L. Day 9 of administration (day of discontinuation): Pain of lower extremities became further aggravated. The patient complained he could not move his legs. CK (CPK) 1339 IU/L. Administration of valsartan was discontinued in the evening. 1 day after discontinuation: CK (CPK) 2251 IU/L, myoglobin 790 ng/mL. Bone scintigraphy was performed to check for muscle disorders. Soft tissue disorder was observed. Internal bleeding-like purpura was seen in the calves and lower legs. 4 days after discontinuation: Leg pain went into remission. Purpura was also going into remission.

				7 days after discontinuation: Leg pain remained only when the patient moved. 11 days of discontinuation: CK (CPK) 267 IU/L. 15 days of discontinuation: Pain of lower extremities almost disappeared; however, the patient complained that the skin on his hands had started to peel 2 to 3 days before. 25 days after discontinuation: Pain of lower extremities appeared when the patient walked for a long distance. No change or aggravation was seen in the patient's hands with peeled skin. 219 days after discontinuation: The patient was able to walk for a long distance. Outcome: The patient recovered.
	Concomitant medications: bisoprolol fumarate, amlodipine besilate, doxazosin mesilate, furosemide, famotidine, magnesium oxide			

Clinical Laboratory Values

	Day 1 of administration	Day 6 of administration	Day 9 of administration (day of discontinuation)	1 day after discontinuation	4 days after discontinuation	6 days after discontinuation	11 days after discontinuation	25 days after discontinuation
CK (CPK) (IU/L)	174	321	1339	2251	1050	637	267	90
CK isoenzymes MB (%)	-	-	-	2	-	-	-	-
CK isoenzymes MM (%)	-	-	-	98	-	-	-	-
Myoglobin (ng/mL)	-	-	-	790	-	-	-	-
RBC ($\times 10^4/mm^3$)	509	442	464	-	467	463	466	437
Hemoglobin (g/dL)	15.7	13.4	14.1	-	14.1	14.0	14.2	13.3
Hematocrit (%)	47.7	41.2	43.4	-	-	43.6	-	-
WBC ($/mm^3$)	8300	8400	8700	-	8000	7700	7700	6900
PLT ($\times 10^4/mm^3$)	21.6	21.3	25.5	-	-	30.9	29.2	-
AST (GOT) (IU/L)	23	24	39	51	42	36	33	23
ALT (GPT) (IU/L)	16	19	34	43	58	60	61	31
Al-P (IU/L)	246	246	271	-	297	293	314	-
LDH (IU/L)	248	247	254	263	266	249	252	198
Total bilirubin (mg/dL)	0.32	0.44	0.30	-	0.35	0.27	0.30	-
BUN (mg/dL)	20.5	16	22.4	17.8	-	22.6	23.4	17.3
Creatinine (mg/dL)	1.12	1.16	1.27	1.13	1.35	1.33	1.43	1.22
Blood glucose（mg/dL）	132	91	100	-	-	108	-	114
Serum potassium (mEq/L)	4.0	4.4	4.7	4.8	4.8	4.9	4.9	4.4
Serum sodium (mEq/L)	139.6	139.3	138.9	136.6	138	137.8	137.9	140.8

CK (CPK): Creatine kinase (Creatine phosphokinase), CK isoenzymes MB: Creatine kinase isoenzymes MB, CK isoenzymes MM: Creatine kinase isoenzymes MM, RBC: Red blood cell count, WBC: White blood cell count, PLT: Platelet, AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), Al-P: Alkaline phosphatase, LDH: Lactate dehydrogenase, BUN: Blood urea nitrogen

2 Yokukansan

Brand Name (name of company)	TSUMURA Yokukansan Extract Granules for Ethical Use (Tsumura & Co.) OHSUGI Yokukansanryo Extract Granule (Tokiwa Pharmaceutical Co., Ltd.)
Therapeutic Category	Kampo medicines
Indications	Following symptoms in patients with delicate constitution and nervousness: neurosis, insomnia, night cry in children, and peevishness in children

≪PRECAUTIONS (underlined parts are additions)≫

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: If abnormalities including pyrexia, cough, dyspnoea, and abnormal chest sound occur, administration of this drug should be discontinued, and then examinations such as chest X-rays and chest CT scans should be performed immediately. Further, appropriate measures such as administration of adrenal corticosteroids should be taken.

Hepatic dysfunction, jaundice: Hepatic dysfunction with significant elevations of AST (GOT), ALT (GPT), Al-P and/or γ-GTP or jaundice may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug 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 May 25, 2010):

- Interstitial pneumonia: 4 cases (no fatalities)
- Hepatic dysfunction, jaundice: 3 cases (no fatalities)

The number of patients treated with this drug per year estimated by MAH: approximately 190,000 (for FY 2009)

Marketed in Japan in: October 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Depression (Hypertension, hyperlipidemia)	7.5g for 305 days	**Interstitial pneumonia** Day 291 of administration: The patient complained that he recently had severe shortness of breath at the time of his periodic visit. On the same day, Chest X-P showed diffuse inflammation images in both lung fields. Day 297 of administration: The patient was diagnosed with interstitial pneumonia based on chest CT. Day 305 of administration (day of discontinuation): Discontinuation of this drug was instructed. 14 days after discontinuation: The patient said breathing became a little easier. 18 days after discontinuation: Chest CT performed at the respiratory department showed reducing tendency of pneumonia shadow. 42 days after discontinuation: Chest X-P showed no aggravating tendency.
	Concomitant medications: perospirone hydrochloride, brotizolam, pravastatin sodium, nateglinide, telmisartan, roxatidine acetate hydrochloride, amlodipine besilate, magnesium oxide			

Clinical Laboratory Values

	Day 262 of administration	18 days of discontinuation
WBC (/mm^3)	7300	6500
LDH (IU/L)	-	244
KL-6 (U/mol)	-	1393
SP-D (ng/mL)	-	214.2

WBC: White blood cell count, LDH: Lactate dehydrogenase, KL-6: Sialylated carbohydrate antigen KL-6, SP-D: Surfactant protein D

Immunoserological test

	18 days of discontinuation
Antinuclear antibody	Negative
Anti SS-A/Ro antibodies	Negative
Anti SS-B/La antibodies	Negative

SS: Sjögren's syndrome

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 30s	Anxiety neurosis (Bronchial asthma, spondylolisthesis)	2.5g for 63 days	**Hepatic dysfunction** 14 days before administration: The patient was diagnosed with asthma at the first visit. Administration of medications such as theophylline, montelukast sodium, famotidine, prednisolone, and clarithromycin was started 7 days before administration: Administration of saibokuto 7.5 g TID was started. Day 1 of administration: Administration of yokukansan was started at 2.5 g/day (before bedtime). Asthma had been difficult to control. Day 51 of administration: Asthma attack went into remission at around this time. Day 60 of administration: Queasy, anorexia, and malaise occurred from around this time. Day 62 of administration: The patient visited the hospital, and a blood sample was collected. Day 63 of administration (day of discontinuation): The patient was contacted by telephone. Administrations of all medications were discontinued in the evening. 1 day after discontinuation: The patient was admitted to the hospital. 10 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: saibokuto, theophylline, montelukast sodium, famotidine, mequitazine, fudosteine, clarithromycin, tulobuterol, sodium cromoglicate, procaterol hydrochloride hydrate, beclometasone dipropionate, betamethasone/*d* -chlorpheniramine maleate			

Clinical Laboratory Values

	Day 62 of administration	1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	6 days after discontinuation	8 days after discontinuation	10 days after discontinuation
AST (GOT) (IU/L)	1156	1194	907	748	294	134	74
ALT (GPT) (IU/L)	1611	1915	1618	1455	804	454	286
Al-P (IU/L)	584	657	576	-	-	-	-
γ-GTP (IU/L)	364	344	287	-	-	-	-
LDH (IU/L)	781	706	-	419	233	-	152
Total bilirubin (mg/dL)	-	2.1	-	1.4	1.0	-	0.7
Direct bilirubin (mg/dL)	-	1.3	-	0.8	0.5	-	0.3

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), Al-P: Alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, LDH: Lactate dehydrogenase

DLST	12 days after discontinuation
Yokukansan	Positive
Saibokuto	Positive

DLST	12 days after discontinuation
Famotidine	Negative
Clarithromycin	Negative

3

Revision of Precautions (No. 218)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated July 6, 2010 (excluding those presented in "2. Important Safety Information" of this Bulletin).

[Brand name]: Major product names are showed.

1

<Antiepileptics>

Phenytoin
Phenytoin/Phenobarbital
Phenytoin/Phenobarbital/Caffeine and Sodium Benzoate
Phenytoin Sodium

[Brand Name]

ALEVIATIN Powder 10%, ALEVIATIN Tablet 25 mg, 100 mg (Dainippon Sumitomo Pharma Co., Ltd.)
ALEVIATIN with PHENOBARBITAL Tablet (Dainippon Sumitomo Pharma Co., Ltd.)
HYDANTOL D COMBINATION TABLETS, E COMBINATION TABLETS, F COMBINATION TABLETS (Fujinaga Pharm Co., Ltd.)
ALEVIATIN Injection 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Neuroleptic malignant syndrome: Neuroleptic malignant syndrome may occur. Patients should be carefully monitored and if symptoms such as pyrexia, disturbances in consciousness, muscle rigidity, involuntary movement, sweating, and tachycardia occur, appropriate measures such as discontinuation of this drug, cooling the body, fluid replacement, and respiratory management should be taken. Increases in white blood cell count and serum CK (CPK) are often observed in association with neuroleptic malignant syndrome, and renal function may decrease accompanied by myoglobinuria.

2

<Contraceptives>

Desogestrel/Ethinylestradiol
Norethisterone/Ethinylestradiol (preparations with the indication for contraception)
Levonorgestrel/Ethinylestradiol

[Brand Name]

Marvelon Tablet 21, Marvelon Tablet 28 (Schering-Plough K.K.)
ORTHO M-21 Tablets (Janssen Pharmaceutical K.K.), Norinyl T28 Tablets (Kaken Pharmaceutical Co., Ltd.)
ANGE 21 TABLETS, ANGE 28 TABLETS (ASKA Pharmaceutical Co., Ltd.)

[Careful Administration]

Women with history of breast cancer

3 <Hemostatics>

Protamine Sulfate

[Brand Name] Novo-Protamine Sulfate 100 mg for I.V. Injection (Mochida Pharmaceutical Co., Ltd.)

[Important Precautions] Patients who have been treated with this drug or protamine-containing insulin may be sensitized to protamine, and it has been reported that such patients may also be prone to shock and anaphylactoid symptoms associated with administration of this drug. Prior to administration of this drug, a careful questioning about previous cardiac catheter test or heart surgery and previous treatment with insulin, for which protamine might have been used, should be performed. This drug should be administered carefully to patients with such history.

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms**: Shock and anaphylactoid symptoms may occur immediately after administration of this drug. Patients should be carefully monitored. If abnormalities such as decreased blood pressure, abnormal pulse, cold sweat, dyspnoea, redness, or depressed level of consciousness are observed, administration of this drug should be discontinued immediately and appropriate measures, such as maintaining blood pressure, fluid replacement/management, and maintaining the airway, should be taken.

4 <Anticoagulants>

Enoxaparin Sodium

[Brand Name] Clexane 2000 IU S.C. Inj. Kit. (sanofi-aventis K.K.)

[Important Precautions] In the following cases, risks of nerve disorders increase.

- Patients who have undergone spinal operation or have spinal deformity
- Postoperative catheter placement
- Concomitant use of drugs that affect haemostasis (e.g., nonsteroidal anti-inflammatory drugs)
- Needle or catheter insertion accompanied with vascular injuries, or frequent needle insertion

5 <Antimetabolites>

Tegafur/Gimeracil/Oteracil Potassium

[Brand Name] TS-1 combination capsule T20, T25, TS-1 combination granule T20, T25 (Taiho Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Myocardial infarction, angina pectoris, arrhythmia, cardiac failure**: Myocardial infarction, angina pectoris, arrhythmia (including ventricular tachycardia), or cardiac failure may occur. Patients should be carefully monitored, and if symptoms such as chest pain, syncope, palpitations, abnormal electrocardiogram, or shortness of breath are observed, administration of this drug should be discontinued and appropriate measures should be taken.

6

<Over the counter drugs>

Yokukansan

[Brand Name] AROPANOL Tablet (Nippon Zenyaku Kogyo Co., Ltd.)

[Consultation] If you experience any of the following symptoms after taking the product, immediately discontinue the use of this drug, and take this leaflet with you and consult with your physician or pharmacist. In rare instances, the following serious symptoms may occur. In such a case, seek immediate medical attention.

Interstitial pneumonia: Shortness of breath, dyspnea, or pyrexia etc. accompanying cough may occur.

Hepatic dysfunction: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

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 July 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorisation holder	Date of EPPV initiate
Tosufloxacin Tosilate Hydrate OZEX fine granules 15% for pediatric use	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*[1]	Abbott Japan Co., Ltd.	January 20, 2010
Infliximab (Recombinant) REMICADE for I.V. Infusion 100*[2]	Mitsubishi Tanabe Pharma Corp.	January 20, 2010
Nonacog Alfa (Genetical Recombination) BeneFIX Intravenous 500, 1000, 2000	Pfizer Japan Inc.	January 20, 2010
Fentanyl Durotep MT Patch 2.1 mg, 4.2 mg, 8.4 mg, 12.6 mg, 16.8 mg*[3]	Janssen Pharmaceutical K.K.	January 20, 2010
Pramipexole Hydrochloride Hydrate BI•Sifrol Tablets 0.125 mg, 0.5 mg*[4]	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, 0.5 g, Meropen Kit for Intravenous Drip Infusion 0.5 g*[5]	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 conjugated vaccine (absorbed) Prevenar Suspension Liquid for S.C. Injection	Pfizer Japan Inc.	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	Daiichi Sankyo	April 16, 2010

REZALTAS COMBINATION TABLETS LD, HD	Company, Limited.	
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
Metformin hydrochloride Metgluco Tablets 250 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 10, 2010
Thalidomide THALED capsule 50	Fujimoto Pharmaceutical Corporation	May 25, 2010
Epoetin Kappa (Genetical Recombination) [Epoetin Alfa Biosimilar 1] Epoetin Alfa BS Injection 750 syringe [JCR], Epoetin Alfa BS Injection 1500 syringe [JCR], Epoetin Alfa Injection 3000 syringe [JCR], Epoetin Alfa BS Injection 750 [JCR], 1500 [JCR], 3000 [JCR]	JCR Pharmaceuticals Co., Ltd.	May 27, 2010
Travoprost/Timolol Maleate DuoTrav Combination Ophthalmic Solution	Alcon Japan Ltd.	June 11, 2010
Dorzolamide Hydrochloride/Timolol Maleate COSOPT Ophtalmic Solution	Banyu Pharmaceutical Co., Ltd.	June 11, 2010
Eculizumab (Genetical Recombination) Soliris Intravenous Drip Infusion 300 mg	Alexion Pharmaceuticals, Inc.	June 14, 2010
Alogliptin Benzoate NESINA Tablets 6.25 mg., 12.5 mg., 25 mg.	Takeda Pharmaceutical Company Limited	June 15, 2010
Candesartan Cilexetil/Amlodipine Besilate UNISIA Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 15, 2010
Panitumumab (Genetical Recombination) Vectibix Intravenous Drip Infusion 100 mg	Takeda Pharmaceutical Company Limited	June 15, 2010
Pregabalin Lyrica Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010
Fentanyl Citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	June 24, 2010

*1 An additional indication for “treatment of patients with psoriasis vulgaris or psoriasis arthropathica, which is not adequately responsive to conventional therapies”

*2 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”

*3 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)”

*4 An additional indication for “treatment of patients with moderate to severe idiopathic restless leg syndrome”

*5 An additional indication for “treatment of patients with febrile neutropenia”