Pharmaceuticals and Medical Devices Safety Information

No. 224 May 2006

Table of Contents

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).

Published by
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Translated by
Pharmaceuticals and Medical Devices Agency

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No. 224 May 2006

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	**Lancing devices (component adjacent to a needle is not disposable) for obtaining blood samples**	*P*	In response to an outbreak of hepatitis B that occurred in a nursing home in UK, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that a link with lancing devices (component adjacent to a needle is not disposable) for obtaining blood samples is suspected. At the same time, the agency also promoted awareness regarding use of lancing devices for obtaining blood samples among healthcare professionals and care workers. In Japan, awareness had been promoted already by including statements such as "Not to be shared among different people" in package inserts. MHLW decided to take preventive measures in order to ensure safety when using these devices and to revise PRECAUTIONS section in package inserts, etc. The content of these measures is presented.	3
2	**Aspirin (excepting enteric coated tablet) (preparations with the indication for Kawasaki disease) (and 5 others)**	*P* *C*	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. 223).	6
3	**(1) Piperidolate Hydrochloride (and 7 others)** **(2) Implantable cardiac pacemakers and implantable cardioverter defibrillators (interactions with the so-called smart key systems)**		Revision of PRECAUTIONS (No. 175)	31
4	**Products subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of May 1, 2006.	35

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

1

Handling of lancing devices (component adjacent to a needle is not disposable) for obtaining blood samples

1. Outline

Lancing devices for obtaining blood are devices that are used for attaching lancing needles for the purpose of obtaining small amounts of samples of blood for glucose testing. There are 3 types of these kinds of devices: ① those where the entire device is disposable[1)], ② those wherein a component adjacent to the needle[2)] is disposable, and ③ those wherein a component adjacent to the needle is not disposable (refer to the **Figure**).

In November 2005, the Medicines and Healthcare products Regulatory Agency (MHRA) announced that there is a suspicion that the type of lancing devices wherein a component adjacent to the needle is not disposable (4 products) was linked to the outbreak of hepatitis B (which resulted in the deaths of 2 people) at a nursing home in UK. At the same time, the agency also promoted awareness by suggesting that healthcare professionals and care workers use lancing devices that are suited for them (specifically, types wherein a component adjacent to the needle is disposable) or use types where the entire devices is disposable. In addition, Health Canada also promoted the same kind of awareness as UK in January 2006.

In Japan, with regard to the type wherein a component adjacent to the needle is not disposable (hereinafter referred to as "this device"; refer to the **Table**), awareness has been promoted through including statements such as "Not to be shared among different people" in the CONTRAINDICATION section and the WARNING section, etc. in package inserts. In addition, case examples of infections suspected to be resulting from this device have not yet been reported in Japan.

However, MHLW decided to take preventive measures in order to ensure safety when using this device and to revise PRECAUTIONS section in package inserts, etc. The content of these measures that were conveyed to manufactures and medical organizations is presented.

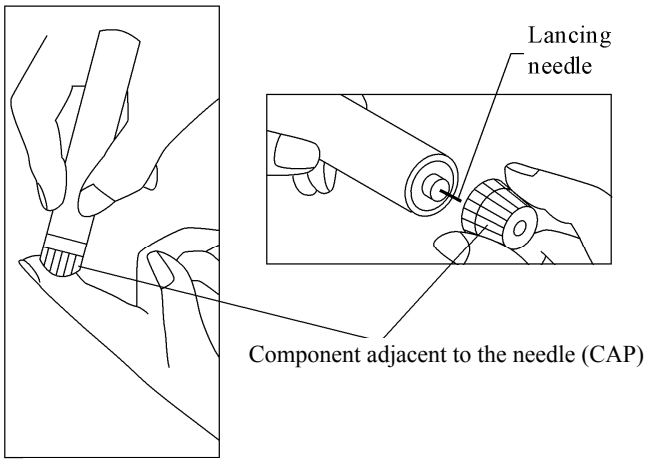

Figure: Lancing devices for obtaining blood samples

Note 1) Refers to the devices that are disposed of after 1 use, and are replaced with a new device.

Note 2) Refers to the end of the device that comes in contact with the skin and that is built to adjust the penetration depth. Also referred to as the endcap.

Table. List of lancing devices for obtaining blood samples that are not types wherein a component adjacent to the needle is disposable

	Manufacturer	Product name
1	ARKRAY Factory, Inc.	Multi-Lancet for Arm
2	ARKRAY Factory, Inc.	Finelet
3	ARKRAY Factory, Inc.	Multi-Lancet II
4	ARKRAY Factory, Inc.	Multi-Lancet S
5	Abbott Japan Co., Ltd.	EasyTouch
6	Abbott Japan Co., Ltd.	Lancet Device
7	Johnson & Johnson K.K.	OneTouch UltraSoft
8	TERAMECS Co., Ltd.	Auto Lancet II
9	NIPRO CORPORATION	NIPRO FreeStyle Lightshot
10	NIPRO CORPORATION	NIPRO FreeStyle Lightshot FLASH
11	NIPRO CORPORATION	FreeStyle Kissei Lancing Device
12	NIPRO CORPORATION	FreeStyle FLASH Kissei Lancing Device
13	NIPRO CORPORATION	Laklet
14	Nippon Becton Dickinson Company, Ltd.	Acelet
15	Bayer Medical Limited	Microlet
16	Bayer Medical Limited	Microlet Choice
17	Roche Diagnostics K.K.	Softclix (lancing device)
18	Roche Diagnostics K.K.	Softclix Plus
19	Roche Diagnostics K.K.	Softclix Mini
20	Roche Diagnostics K.K.	Multiclix

This table contains information that is current as of February 23, 2006.

2. Actions should be taken by manufacturers

Manufacturers must make revisions to the package inserts regarding the following matters.

① The statement “Limited to individual use, must not be used among multiple patients” must be included in the CONTRAINDICATIONS section.

② In addition to attaching a sticker indicating “Not intended for use on multiple patients” before releasing the products, the manufacturer must distribute the same sticker to delivery destinations and request that the stickers be attached to products that have already been delivered but for which a sticker has not been attached.

3. Actions should be taken by medical institutions, etc.

Medical institutions must take particular precautions not to use devices wherein a component adjacent to the needle is not disposable among multiple patients.

(References)

MHLW website
http://www.mhlw.go.jp/houdou/2006/03/h0303-3.html (in Japanese)

MHRA website
http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON2022643

Health Canada website
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_04_e.html

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. 223).

1 Aspirin (excepting enteric coated tablet) (preparations with the indication for Kawasaki disease), Aspirin (excepting enteric coated tablet) (preparations without the indication for Kawasaki disease), Aspirin/Ascorbic Acid, Aspirin/Dialuminate (330 mg), Aspirin (enteric coated tablet), Aspirin/Dialuminate (81 mg)

❶Aspirin (excepting enteric coated tablet) (preparations with the indication for Kawasaki disease)

Brand Name (name of Company)	Aspirin "Bayer" (Bayer Yakuhin, Ltd.) Aspirin "Hoei" (Merck Hoei Ltd.) Aspirin "Metaru" (Nakakita Co., Ltd.) Aspirin "Yoshida" (Yoshida Pharmaceutical Co., Ltd.)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	① Chronic rheumatoid arthritis, rheumatic fever, osteoarthritis, ankylosing spondylitis, periarthritis, fibrositis, postoperative pain, toothache, symptomatic neuralgia, arthralgia, low back pain, myalgia, sprain pain, bruise pain, pain from gout, headache, algomenorrhea ② Pyretolysis and pain relief for the following disease Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanying acute bronchitis) ③ Kawasaki disease (including cardiovascular sequelae due to Kawasaki disease)

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

[Contraindications]

Pregnant women who are expecting within 12 weeks

[Adverse Reactions (clinically significant adverse reactions)]

Aplastic anaemia, platelets decreased, white blood cell decreased: Aplastic anaemia, platelets decreased, and white blood cell decreased may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

Haemorrhage:

Haemorrhage intracranial including cerebral haemorrhage: Haemorrhage intracranial including cerebral haemorrhage (initial symptoms: headache, nausea/vomiting, consciousness disturbed, hemiplegia, etc.) may occur. Patients should be carefully monitored. Discontinue administration and take appropriate measures in such cases.

Pulmonary haemorrhage, haemorrhage including digestive tract, epistaxis, ocular fundus bleeding: Pulmonary haemorrhage, haemorrhage of digestive tract, epistaxis, and ocular fundus bleeding may occur. Patient should be carefully monitored. Discontinue administration and take appropriate measures in such cases.

Hepatic function disorder, jaundice: Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), and γ-GTP levels, etc. and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed,

appropriate measures, such as discontinuation of administration, should be taken.
Peptic ulcer, small intestinal ulcer, large intestinal ulcer: Peptic ulcers such as gastric ulcers/duodenal ulcers with melaena may occur. Also, small intestinal ulcer and large intestinal ulcer with haemorrhage of the digestive tract and intestinal perforation may occur. Patients should be carefully monitored. If abnormalities are observed, discontinue administration and take appropriate measures.

❷ Aspirin (excepting enteric coated tablet) (preparations without the indication for Kawasaki disease), Aspirin/Ascorbic Acid, Aspirin/Dialuminate (330 mg)

Brand Name (name of company)	**Aspirin (excepting enteric coated tablet) (preparations without the indication for Kawasaki disease)** Aspirin (KENEI Pharmaceutical Co., Ltd.) Aspirin (Maruishi Pharmaceutical Co., Ltd.) Aspirin (Tokai Pharmaceutical Co., Ltd.) Aspirin (Yamazen Corporation) Aspirin (Sanko) (Kyowa Iryo Kaihatsu Co., Ltd.) Aspirin "Ebisu" (Ebisu Pharmaceutical. Co.) Aspirin "Tsukishima" (Tsukishima Pharmaceutical Co., Ltd.) Aspirin "Hishiyama" (Nipro Pharma Corporation) Aspirin OY (Oriental Pharmaceutical Co., Ltd.) Aspirin Sioe (Sioe Pharmaceutical Co., Ltd.) "JUNSEI" Aspirin (Junsei Chemical Co., Ltd.) Salitison Supp. 750 (Showa Yakuhin Kako Co., Ltd.) **Aspirin/Ascorbic acid** E-A-C Tablets (Toyama Chemical Co., Ltd.) **Aspirin/Dialuminate (330 mg)** Iskia Tablets 330 mg (Shiono Chemical Co., Ltd.) Bassamin Tablets 330 mg (Taiyo Yakuhin Co., Ltd.) Bufferin 330 mg Tablets (Lion Corporation)
Therapeutic Category	Antipyretics and analgesics, anti-inflammatory agents
Indications	**Aspirin (excepting enteric coated tablet) (preparations without the indication for Kawasaki disease)** (oral dosage form) ① Chronic rheumatoid arthritis, rheumatic fever, osteoarthritis, ankylosing spondylitis, periarthritis, fibrositis, postoperative pain, toothache, symptomatic neuralgia, arthralgia, low back pain, myalgia, sprain pain, bruise pain, pain from gout, headache, algomenorrhea ② Pyretolysis and pain relief for the following disease Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanying acute bronchitis) (Salitison Supp. 750) ① Toothache, chronic rheumatoid arthritis, rheumatic fever, osteoarthritis, ankylosing spondylitis, periarthritis, postoperative pain, symptomatic neuralgia, arthralgia, low back pain, myalgia, sprain pain, bruise pain, pain from gout, headache, algomenorrhea ② Pyretolysis and pain relief for the following disease Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanying acute bronchitis) **Aspirin/Ascorbic acid** Alleviation of fevers from common cold, chronic rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, osteoarthritis, fibrositis, arthralgia, low back pain, symptomatic neuralgia **Aspirin/Dialuminate (330 mg)** Headache, toothache, algomenorrhea, alleviation of fevers from common colds, chronic rheumatoid arthritis, rheumatic fever, symptomatic neuralgia

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

[Contraindications]	Pregnant women who are expecting within 12 weeks

[Adverse Reactions (clinically significant adverse reactions)]

Aplastic anaemia, platelets decreased, white blood cell decreased: Aplastic anaemia, platelets decreased, and white blood cell decreased may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

Haemorrhage:

Haemorrhage intracranial including cerebral haemorrhage.: Haemorrhage intracranial including cerebral haemorrhage, (initial symptoms: headache, nausea/vomiting, consciousness disturbed, hemiplegia, etc.) may occur. Patients should be carefully monitored. Discontinue administration and take appropriate measures in such cases.

Pulmonary haemorrhage, haemorrhage including digestive tract, epistaxis, ocular fundus bleeding: Pulmonary haemorrhage, haemorrhage of digestive tract, epistaxis, and ocular fundus bleeding may occur. Patient should be carefully monitored. Discontinue administration and take appropriate measures in such cases.

Hepatic function disorder, jaundice: Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), and γ-GTP levels, etc. and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.

Peptic ulcer, small intestinal ulcer, large intestinal ulcer: Peptic ulcers such as gastric ulcers/duodenal ulcers with melaena may occur. Also, small intestinal ulcer and large intestinal ulcer with haemorrhage of the digestive tract and intestinal perforation may occur. Patients should be carefully monitored. If abnormalities are observed, discontinue administration and take appropriate measures.

❸ Aspirin (enteric coated tablet), Aspirin/Dialuminate (81 mg)

Brand Name (name of company)	**Aspirin (enteric coated tablet)** Aspirin Tablets 100 "KN" (Kobayashi Kako Co., Ltd.) Aspirin Enteric Tab. 100 mg "Merck" (Merck Hoei Ltd.) Zenaspirin Tablets 100 (Zensei Pharmaceutical Industries Co., Ltd.) Nichiaspirin Tablets 100 (Nichi-iko Pharmaceutical Co., Ltd.) Bayaspirin Tablets 100 mg (Bayer Yakuhin, Ltd.) **Aspirin/Dialuminate (81 mg)** Asphanate Tablets 81 mg (Nakakita Co., Ltd.) Nitogis Tablets 81 mg (Shiono Chemical Co., Ltd.) Bassamin Tablets 81 mg (Taiyo Yakuhin Co., Ltd.) Bufferin 81 mg Tablets (Lion Corporation) Famoter 81 mg Tablets (Tsuruhara Pharmaceutical Co., Ltd.)
Therapeutic Category	Blood and body fluid agents-Miscellaneous
Indications	① Suppression of thrombus and embolus formation resulting from the following diseases Angina pectoris (chronic stable angina, unstable angina) Myocardial infarction Ischemic cerebrovascular disorder (transient ischaemic attacks (TIA), cerebral infarction) ② Suppression of thrombus and embolus formation resulting from coronary artery bypass grafting (CABG) or percutanerous transluminal coronary angioplasty (PTCA) ③ Kawasaki disease (including cardiovascular sequelae due to Kawasaki disease) (However, ③ does not apply for Aspirin Tablets 100 "KN", Aspirin Enteric Tab. 100 mg "Merck", Zenaspirin Tablets 100, and Nichiaspirin Tablets 100)

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

[Adverse Reactions (clinically significant adverse reactions)]

Aplastic anaemia, platelets decreased, white blood cell decreased: Aplastic anaemia, platelets decreased, and white blood cell decreased may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

Hepatic function disorder, jaundice: Hepatic function disorder with significant elevations of AST (GOT), ALT (GPT), and γ-GTP levels, etc. and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

Peptic ulcer, small intestinal ulcer, large intestinal ulcer: Peptic ulcers such as gastric ulcers/duodenal ulcers with melaena may occur. Also, small intestinal ulcer and large intestinal ulcer with haemorrhage of the digestive tract and intestinal perforation may occur. Patients should be carefully monitored. If abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information>

With regard to ❶ to ❸,
the number of reported adverse reaction cases in about the last 3 years (April 2003 to December 2005) (events for which a causality to the drug could not be denied)

- Platelets decreased: 5 cases (no fatal case)
- White blood cell decreased: 2 cases (no fatal case)
- Hepatic function disorder, jaundice: 11 cases (of which 1 had a fatal case)
- Peptic ulcer, small intestinal ulcer, large intestinal ulcer: 9 cases (no fatal case)

The number of patients treated with Aspirin for a year estimated by MAH (Marketing Authorisation Holder): approximately 5.2 million (FY2005)
Marketed in Japan in: For ❶ and ❷, 1951
For ❸, December 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 60s	Myocardial ischaemia (chronic renal failure, peritoneal dialysis)	100 mg 63 days	**Thrombocytopenia** Medical history: parathyroidectomy Medical history of adverse reaction: urticaria caused by alfacalcidol On day 1 of administration: Administration of this drug and nicorandil was initiated. On day 15 of administration: Administration of warfarin potassium was initiated. On day 43 of administration: Administration of isosorbide mononitrate was initiated. On day 58 of administration: Skin eruption developed in chest area. It was gradually expanded afterwards. On day 63 of administration (day of discontinuation): Administration of this drug and isosorbide mononitrate was discontinued based on the patient's own judgment. 4 days after discontinuation: As there was persistent pyrexia (38°C), the patient was hospitalized for detailed examination. Administration of cetirizine hydrochloride, mometasone furoate lotion, white petrolatum, glycyrrhizin/glycine/cysteine was initiated for skin eruption. Platelet count was $10 \times 10^4/mm^3$.	Company report

				8 days after discontinuation: Platelets decreased developed (platelet count 3 × 10^4/mm^3). 23 days after discontinuation: Platelet count improved (platelet count 17.4 × 10^4/mm^3). 38 days after discontinuation: Skin eruption disappeared. DLST: Both this drug and isosorbide mononitrate negative.	
	Concomitant medications: isosorbide mononitrate, nicorandil, warfarin potassium, ranitidine hydrochloride, etodolac, nitrazepam, sennoside, potassium chloride, sodium azulene sulfonate/L-glutamine, prednisolone				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Transient ischaemic attack (unclear)	81 mg 64 days	**Agranulocytosis** On day 1 of administration: Administration of this drug (aspirin/dialuminate) was initiated. On day 59 of administration: Pyrexia and pain pharynx were noted. On day 64 of administration (day of discontinuation): White blood cell count was 500/mm^3. 1 day after discontinuation: The patient was hospitalized. Administration of 75 μg/day of filgrastim (Genetical recombination) was initiated. Antibiotics were used concomitantly. For bone marrow, granulocytes and their progenitor cells disappeared. 21 days after discontinuation: The patient did not recover. Filgrastim (Genetical recombination) was increased to 150 μg/day. 42 days after discontinuation: Pneumonia was concomitantly developed. 44 days after discontinuation: Oral administration of ifenprodil tartrate was discontinued. 56 days after discontinuation: The patient did not recover. Jaundice and pneumonia aggravated. 60 days after discontinuation: The patient developed respiratory failure. Steroid pulse therapy was started with methylprednisolone sodium succinate. 65 days after discontinuation: Neutrophils were observed in peripheral blood. The patient was transferred to ICU. Artificial respirator was used. 66 days after discontinuation: Despite complete recovery of white blood cells, no changes were observed in jaundice and pneumonia. 69 days after discontinuation: The patient died from multi-organ failure.	Company report
	Concomitant medications: ifenprodil tartrate, ticlopidine hydrochloride, nicergoline				

Clinical Laboratory Values

	Approx. 2 months before administration	1 day after discontinuation	21 days after discontinuation	42 days after discontinuation	44 days after discontinuation	56 days after discontinuation	60 days after discontinuation	65 days after discontinuation	66 days after discontinuation	69 days after discontinuation
WBC (/mm^3)	5500	600	1300	900	1000	800	400	800	2200	15900
Neutrophils (%)	--	0	0	6	1	2	1	77	64	--
PLT ($\times 10^4$/mm^3)	30.2	29.0	45.4	40.1	39.3	25.1	17.5	2.9	2.5	1.7
AST (GOT) (IU/L)	30	26	116	122	101	110	174	31	38	72
ALT (GPT) (IU/L)	27	39	164	150	137	94	205	44	37	42
Al-P (IU/L)	162	665	463	1350	1333	812	688	240	176	--
LDH (IU/L)	405	201	256	549	486	372	421	494	536	962
γ-GTP (IU/L)	54	375	421	596	516	161	181	54	36	--
Total bilirubin (mg/dL)	0.9	2.4	0.5	1.0	1.3	3.2	6.7	12.9	14.2	18.8
Serum creatinine (mg/dL)	--	1.0	1.0	0.8	0.9	0.9	0.8	1.0	1.2	--

WBC: White Blood Cell
PLT: Platelet
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 50s	Thrombosis prophylaxis (hypertension, angina pectoris, diabetes mellitus)	81 mg 1837 days	**Liver disorder** On day 1 of administration: Administration of this drug (aspirin/dialuminate) was initiated. Approx. on day 1830 of administration: Anorexia developed. On day 1837 of administration (day of discontinuation): In a blood test, there were findings of severe hepatitis, based on AST (GOT) 2650 IU/L, ALT (GPT) 5030 IU/L, and total bilirubin 6.14 mg/dL. The patient was hospitalized. After hospitalization, oral administration of this drug, voglibose, gliclazide, amlodipine besilate, isosorbide dinitrate, and diltiazem hydrochloride was discontinued. Through drip infusion treatment, AST (GOT) and ALT (GPT) gradually decreased, but jaundice persisted. 3 days after discontinuation: Due to itchy feeling caused by jaundice, hydroxyzine pamoate (3 capsules in total, 3 times a day) was administered. 35 days after discontinuation: Diabetes mellitus control was switched to insulin and hepatic function improved. The patient was discharged from the hospital. DLST: All drugs negative.	Company report
	Concomitant medications: voglibose, gliclazide, amlodipine besilate, isosorbide dinitrate, diltiazem hydrochloride				

Clinical Laboratory Values

	On day 29 of administration	On day 234 of administration	On day 1837 of administration (day of discontinuation)	9 days after discontinuation	19 days after discontinuation	33 days after discontinuation
AST (GOT) (IU/L)	18	21	2650	846	55	14
ALT (GPT) (IU/L)	45	31	5030	1650	188	30
Al-P (IU/L)	471	408	1437	840	612	438
LDH (IU/L)	--	--	2590	407	149	127
γ-GTP (IU/L)	208	219	824	371	221	--
Total bilirubin (mg/dL)	0.45	0.42	6.14	16.49	5.92	2.27
Direct bilirubin (mg/dL)	0.17	0.16	--	--	--	--
BUN (mg/dL)	5.3	17.9	13.2	--	--	12.2
Serum creatinine (mg/dL)	1.17	1.0	0.71			0.87
RBC ($\times 10^4/mm^3$)	480	507	486	494	445	430
Haemoglobin (g/dL)	14.7	15.3	15.1	15.3	13.4	13.1
Haematocrit (%)	43.7	47.0	44.5	44.9	39.6	39.3
WBC ($/mm^3$)	5900	5400	6900	6100	6400	5800
PLT ($\times 10^4/mm^3$)	20.5	17.9	--	--	22.7	22.9

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
Al-P: Alkaline Phosphatase
LDH: Lactate Dehydrogenase
γ-GTP: γ-Glutamyltranspeptidase
BUN: Blood Urea Nitrogen
RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
4	Male 70s	Atrial fibrillation (chronic cardiac failure, hypertension, diabetes mellitus, large intestine carcinoma, bladder cancer)	100 mg 5 days ↓ (no treatment for 32 days) ↓ 100 mg 7 days	**Small intestine perforation, thrombocytopenia** While the patient was hospitalized in the department of internal medicine, large intestine carcinoma and bladder cancer were suspected based on CT findings. 7 days before administration: Administration of multiple drugs prescribed by the department of internal medicine was discontinued. On day 1 of administration: Administration of this drug was initiated. On day 2 of administration: Single administration of 6000 units of epoetin alfa (Genetical recombination). On day 5 of administration (day of discontinuation): Idiopathic small intestine ulcer developed. Abdominal pain and pyrexia confirmed, administration of this drug was discontinued. 7 days after discontinuation: As small intestine (jejunal) ulcer/perforation was confirmed, emergency operation was performed. Operation for large intestine carcinoma was conducted at the same time. 32 days after discontinuation: Administration of vancomycin hydrochloride, propiverine hydrochloride, naftopidil, levofloxacin, and troxipide was initiated.	Company report

				33 days after discontinuation (on day 1 of readministration): Administration of this drug was reinitiated. Administration of digoxin and nizatidine was initiated. On day 2 of readministration: Thrombocytopenia was manifested. On day 7 of readministration (day of discontinuation of readministration) Readministration of this drug was discontinued. 1 day after discontinuation of readministration: Increase in platelet count was confirmed. 4 days after discontinuation of readministration: Recovery of platelet count was confirmed. 26 days after discontinuation of readministration: Operation for bladder cancer was performed.	
	Concomitant medications: verapamil hydrochloride, iron compounds, temocapril hydrochloride, enalapril maleate, voglibose, cilnidipine, furosemide, spironolactone, epoetin alfa (Genetical recombination), vancomycin hydrochloride, propiverine hydrochloride, naftopidil, levofloxacin, troxipide, digoxin, nizatidine				

Clinical Laboratory Values

	31 days after discontinuation	On day 2 of readministration	On day 6 of readministration	On day 7 of readministration (day of discontinuation of readministration)	1 day after discontinuation of readministration	4 days after discontinuation of readministration
PLT ($\times 10^4/mm^3$)	48.4	10.4	0.6	1.4	6.7	20.1

PLT: Platelet

2 Tiquizium Bromide

Brand Name (name of company)	Aspora Capsules 5 and 10 (Takata Seiyaku Co., Ltd.) Advaston Capsules 10 (Taiyo Yakuhin Co., Ltd.) Gastirol Capsules 10 mg (Nihon Pharmaceutical Industry Co., Ltd.) Thiasita Capsules 10 (Maruko Pharmaceutical Co., Ltd.) Thiaton Granules 2%, Thiaton Capsules 5 mg and 10 mg (Abbott Japan Co., Ltd.) Tiapaston Cap. 10 (Towa Pharmaceutical Co., Ltd.) Thiameron Granules, Thiameron Capsules 10 mg (Tsuruhara Pharmaceutical Co., Ltd.) Tinolart Capsule 10 (Taisho Pharmaceutical Industries, Ltd.) Thiwan Capsules 10 (Sawai Pharmaceutical Co., Ltd.) Pukett Capsules (Zensei Pharmaceutical Industries Co., Ltd.) Breiful Capsules 10 (Toyo Pharmar Co., Ltd.)
Therapeutic Category	Autonomic nervous system agents
Indications	Cramps and hyperanacinesia resulting from the following diseases Gastritis, gastric ulcer, duodenal ulcer, enterocolitis, irritable bowel syndrome, gallbladder/biliary tract disease, urolithiasis

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

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities such as blood pressure decreased, dyspnoea, redness, urticaria, and angioedema are observed, administration should be discontinued and appropriate measures should be taken.

Hepatic function disorder, jaundice: Hepatic function disorder with significant elevation of AST (GOT), ALT (GPT), and Al-P levels and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Number of reported adverse reaction cases in about the last 3 years (April 2003 to December 2005) (events for which a causality to the drug could not be denied)

- Shock (including anaphylactic shock): 0 cases (no fatal case)

• Hepatic function disorder, jaundice: 1 case (no fatal case)
The number of patients treated with Tiquizium for a year estimated by MAH: approximately 2.55 million (FY2005)
Marketed in Japan in: 1984
These revisions are made in accordance with results from evaluations conducted upon approval (April 2006) of OTC tiquizium bromide.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 50s	Abdominal pain, gastritis, calculus renal, calculus ureteric, haematuria (liver disorder)	10 mg once	**Anaphylactic shock** Medical history: calculus renal, allergic predisposition Approx. 15 minutes before administration: The patient ate lunch. On day 1 of administration: This drug and concomitant medications were administered for abdominal pain. Approx. 25 minutes after administration: Generalised urticaria and dyspnoea were developed. Approx. 1 hours after administration: Blood pressure decreased (74/47 mmHg). Arterial blood gases were as follows. pH 7.421, $PaCO_2$ 40.5 mmHg, PaO_2 43.4 mmHg, HCO_3 26.3 mEq/L, BE 2.3 mEq/L, SO_2 80.1% The patient had generalized skin rashes and itching. Face oedema developed. Since anaphylactic shock was suspected, treatment through administration of O_2, vasopressor (drug name is unknown), and steroid drug (1000 mg of methylprednisolone sodium succinate for injection) were conducted. Clinical course was monitored through emergency hospitalization. 1 day after discontinuation: Due to improvement in symptoms, administration of vasopressor and O_2 was discontinued. The patient recovered. Remarks: Diathesis of allergies in this patient could not be confirmed. Challenge test was performed. After oral administration of this drug, anaphylaxis was exacerbated again. No particular changes were observed with the 3 other drugs.	Company report
	Concomitant medications: ranitidine hydrochloride, cetraxate hydrochloride, carbazochrome sodium sulfonate				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 40s	Abdominal discomfort (none)	Unknown Approx. 1 month and 5 days	**Jaundice, hepatic function abnormal** Medical history: acute hepatitis, acute pancreatitis On day 1 of administration: This drug and concomitant medications were administered for abdominal discomfort. Approx. on month 1 of administration: Yellowing of urine and abdominal discomfort were developed. Approx. on month 1 and day 3 of administration: As general malaise, anorexia, and nausea worsened, the patient made a hospital visit. He was diagnosed with hepatic function abnormal. Approx. on month 1 and day 4 of administration: The patient was hospitalized. Hepatitis viral markers were all negative. As the result of lymphocyte stimulation test with drugs, only this drug was positive. The patient was treated with glycyrrhizin/glycine/cysteine. Despite a decrease in transaminase value, total bilirubin increased (23.7 mg/dL). Approx. on month 1 and day 5 of administration (day of discontinuation): Administration of this drug and concomitant medications was discontinued. The patient was suddenly improved afterwards. 61 days after discontinuation: The patient recovered.	Company report
	Concomitant medications: biodiastase 2000				

Clinical Laboratory Values

	1 month before administration	Approx. on month 1 and day 5 of administration (day of discontinuation)	52 days after discontinuation	59 days after discontinuation
Eosinophils (%)	--	2	7.4	--
AST (GOT) (IU/L)	22	1395	29	25
ALT (GPT) (IU/L)	22	2268	55	43
Al-P (IU/L)	99	276	103	--
Total bilirubin (mg/dL)	0.7	4.6	2.7	1.7

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

3 Dalteparin Sodium, Parnaparin Sodium, Reviparin Sodium, Heparin Calcium, Heparin Sodium (injectable dosage form) (preparation without the indication for prevention of blood coagulation into indwelling intravenous route), Heparin Sodium (injectable dosage form) (preparation without the indication for prevention of blood coagulation into indwelling intravenous route)

❶ Dalteparin Sodium, Parnaparin Sodium, Reviparin Sodium

Brand Name (name of company)	**Dalteparin Sodium** Dalteparin-Na Syringe 5000 "HK" (Hikari Pharmaceutical Co., Ltd.) Dalteparin Sodium Intravenous 1000 Units/mL "Merck" (Merck Hoei Ltd.) Daltepan Intravenous 5000 (Nichi-iko Pharmaceutical Co., Ltd.) Fragmin IV (Pfizer Japan Inc.)

	Fluzepamin Intravenous 1000 Units/mL (Taiyo Yakuhin Co., Ltd.) Fresubaru IV (Nisshin Pharmaceutical Co., Ltd.) Hepagumin Intravenous 1000 Units/mL (Sawai Pharmaceutical Co., Ltd.) Hepachron Injection 5000 (Sankyo Yell Yakuhin Co., Ltd.) Resolmin Injection 1000 (Ito Life Sciences Inc.) **Parnaparin Sodium** Minihepa Injection 500 (Ito Life Sciences Inc.) Lowhepa Injection 500 (Ajinomoto Co., Inc.) **Reviparin Sodium** Clivarine Injection 1000 (Abbott Japan Co., Ltd.) Lowmorin Inj. (Nihon Schering K.K.)
Therapeutic Category	Anticoagulants
Indications	**Dalteparin Sodium** ① Prevention of blood coagulation of perfused blood in extracorporeal blood circulation (haemodialysis) ② Disseminated intravascular coagulation (DIC) **Parnaparin Sodium** Prevention of blood coagulation of perfused blood in extracorporeal blood circulation (haemodialysis, hemodiafiltration, hemofiltration) **Reviparin Sodium** Prevention of blood coagulation of perfused blood in extracorporeal blood circulation (haemodialysis)

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

[Relative Contraindications]	Patients with a history of heparin-induced thrombocytopenia (HIT)
[Other Precautions]	Heparin-induced thrombocytopenia (HIT) is a pathological condition that is mediated by an immunological mechanism based on the development of autoantibodies (HIT antibodies) against the heparin-PF4 complex, and may accompany serious thrombosis (cerebral infarction, pulmonary embolism, deep vein thrombosis, etc.). It has been reported that the HIT antibodies that develop during the onset of HIT disappear/decrease after approximately 100 days.

❷ Heparin Calcium, Heparin Sodium (injectable dosage form) (preparation without the indication for prevention of blood coagulation into indwelling intravenous route)

Brand Name (name of company)	**Heparin Calcium** Caprocin Injection, Caprocin for S.C. Injection (Sawai Pharmaceutical Co., Ltd.) Heparin Calcium Injection (Ajinomoto Co., Inc.) **Heparin Sodium (injectable dosage form) (preparation without the indication for prevention of blood coagulation into indwelling intravenous route)** Heparin Sodium Injection 250 Units/mL for Dialysis (Fuso Pharmaceutical Industries, Ltd.) Novo-Heparin 1000 Units for Injection (Mochida Pharmaceutical Co., Ltd.) Heparin Na 500 Units/mL Syringe "NP" (Nipro Pharma Corporation) Heparin Sodium Injection (FUSO Pharmaceutical Industries, Ltd.) Heparin Sodium Injection F (Fuji Pharma Co., Ltd.) Heparin Sodium Injection-Wf (Nipro Pharma Corporation) Heparin Sodium Injection "Ajinomoto" (Ajinomoto Co., Inc.) Heparin Sodium Injection N "Ajinomoto" (Ajinomoto Co., Inc.)
Therapeutic Category	Anticoagulants
Indications	**Heparin Calcium** (Caprocin Injection, Heparin Calcium Injection) Prevention of blood coagulation of perfused blood in extracorporeal blood circulation (artificial kidney and heart-lung machine) Treatment of disseminated intravascular coagulation Prevention of blood coagulation when inserting vascular catheter

	Prevention of blood coagulation during blood transfusions and blood tests Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, arterial thromboembolism of the limbs, thromboembolism during/after operations) (Caprocin for S.C. Injection) Treatment of disseminated intravascular coagulation Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, arterial thromboembolism of the limbs, thromboembolism during/after operations) **Heparin Sodium (injectable dosage form) (preparation without the indication for prevention of blood coagulation into indwelling intravenous route)** (Heparin Sodium Injection 250 Units/mL for Dialysis) Prevention of blood coagulation during haemodialysis and use of extracorporeal circuits (Heparin Na 500 Units/mL Syringe "NP") Prevention of blood coagulation during haemodialysis and use of other extracorporeal circuits (Novo-Heparin 1000 Units for Injection, Heparin Sodium Injection, Heparin Sodium Injection F, Heparin Sodium Injection-Wf, Heparin Sodium Injection "Ajinomoto", Heparin Sodium Injection N "Ajinomoto") Treatment of disseminated intravascular coagulation Prevention of blood coagulation during haemodialysis and use of heart-lung machine and other extracorporeal circuits Prevention of blood coagulation when inserting vascular catheter Prevention of blood coagulation during blood transfusions and blood tests Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, arterial thromboembolism of the limbs, thromboembolism during/after operations)

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

[Relative Contraindications]	Patients with a history of heparin-induced thrombocytopenia (HIT)
[Important Precautions]	Heparin-induced thrombocytopenia (HIT) may occur after administration of this drug. HIT is a pathological condition that is mediated by an immunological mechanism based on the development of autoantibodies (HIT antibodies) against the heparin-PF4 complex, and may accompany platelets decreased and serious thrombosis (cerebral infarction, pulmonary embolism, deep vein thrombosis, etc.). After administration of this drug, measure the platelet count, and if a significant decrease in the platelet count or abnormalities suggesting thrombosis are observed, discontinue administration and take appropriate measures.
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities such as blood pressure decreased, consciousness decreased, dyspnoea, cyanosis, and urticaria are observed, discontinue administration and take appropriate measures. **Platelets decreased, platelets decreased and thrombosis accompanying HIT, etc.:** Significant platelets decreased may occur after administration of this drug. In the case of HIT, it is accompanied by a significant platelets decreased, thrombosis such as cerebral infarction, pulmonary embolism, and deep vein thrombosis, shunt occlusion and circuit occlusion. After administration of this drug, measure the platelet count, and if a significant decrease in the platelet count or abnormalities suggesting thrombosis are observed, discontinue administration and take appropriate measures.
[Other Precautions]	It has been reported that the HIT antibodies that develop during the onset of HIT disappear/decrease after approximately 100 days.

❸ Heparin Sodium (injectable dosage form) (preparation with the indication for prevention of blood coagulation into indwelling intravenous route)

Brand Name (name of company)	Deribadex 10 Unit Syringe, 100 Unit Syringe (Shiono Chemical Co., Ltd.) Hepaflush 10 Units/mL Syringe 5 mL and 10 mL, Hepaflush 100 Units/mL Syringe 5 mL and 10 mL (Terumo Corporation) Heparin Na Lock 10 Syringe and 100 Syringe (Mitsubishi Pharma Corporation) Pemiroc 10 Units/mL Syringe, Pemiroc 100 Units/mL Syringe (Taiyo Yakuhin Co., Ltd.)
Therapeutic Category	Anticoagulants
Indications	Prevention of blood coagulation in the intravenous indwelling route

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

[Relative Contraindications]	Patients with a history of heparin-induced thrombocytopenia (HIT)
[Important Precautions]	Heparin-induced thrombocytopenia (HIT) may occur after administration of this drug. HIT is a pathological condition that is mediated by an immunological mechanism based on the development of autoantibodies (HIT antibodies) against the heparin-PF4 complex, and may accompany platelets decreased and serious thrombosis (cerebral infarction, pulmonary embolism, deep vein thrombosis, etc.). After administration of this drug, measure the platelet count, and if a significant decrease in the platelet count or abnormalities suggesting thrombosis are observed, discontinue administration and take appropriate measures.
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities such as blood pressure decreased, consciousness decreased, dyspnoea, cyanosis, and urticaria are observed, discontinue administration and take appropriate measures. **Platelets decreased, platelets decreased and thrombosis accompanying HIT, etc.:** Significant platelets decreased may occur after administration of this drug. In the case of HIT, it is accompanied by a significant platelets decreased, thrombosis such as cerebral infarction, pulmonary embolism, and deep vein thrombosis, shunt occlusion and circuit occlusion. After administration of this drug, measure the platelet count, and if a significant decrease in the platelet count or abnormalities suggesting thrombosis are observed, discontinue administration and take appropriate measures.
[Other Precautions]	It has been reported that the HIT antibodies that develop during the onset of HIT disappear/decrease after approximately 100 days.
<Reference Information>	With regard to ❶, The number of patient treated with Dalteparin, Parnaparin, or Reviparin for a year estimated by MAH: approximately 50000 (FY2005) Marketed in Japan in: May 1992 With regard to ❷ and ❸, Number of reported adverse reaction cases in about the last 3 years (April 2003 to February 2006) (events for which a causality to the drug could not be denied) • Anaphylaxis: 4 cases (no fatal case) The number of patient treated with Heparin for a year estimated by MAH: approximately 4.5 million (FY2005) Marketed in Japan in: 1962 With regard to the HIT in ❶ to❸, awareness has been promoted as "platelets decreased", but revisions have been made as its pathological condition has become clear, and its diagnosis name has become widely used.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Replacement of the ascending aorta and aortic valve due to aortic valve stenosis (hypertension)	10000 units 1 day ↓ (no administration for 3 days) ↓ 3000 units 4 days ↓ 10000 units 1 day	**Heparin-induced thrombocytopenia (HIT)** Medication history of this drug: none On day 1 of administration: The patient had slight chest pain, and 10000 units of this drug were administered. 4 days after discontinuation (On day 1 of readministration): With regard to aortic valve stenosis, there was strong calcification of the aorta. Replacements of the ascending aorta and aortic valve were performed. Readministration of this drug was started. Coronary artery bypass was also performed for myocardial infarction during operation. There was an event that internal pressure increased resulting from blood clots in heart-lung machine during extracorporeal circulation. Duration of extracorporeal circulation was long, and there were difficulties in hemostasis. 26 units of MAP (human red cell concentrate), 40 units of FFP (fresh frozen human plasma), 30 units of PC (human platelet concentrate) were administered, and the patient was put into ICU. After patient was put into ICU, platelet count was low, at $1.3 \times 10^4/mm^3$, and as it decreased to $0.8 \times 10^4/mm^3$, platelet concentrate was administered, and platelet count recovered to $11.0 \times 10^4/mm^3$. On day 3 of readministration: Since platelet count decreased to $1.1 \times 10^4/mm^3$, 20 units of human platelets concentrate were administered. On day 4 of readministration: Since hemodynamics became stable and administration of sedatives was discontinued, paralysis of the patient's right lower half was confirmed. On day 5 of readministration (day of discontinuation of readministration): Even after the administration of 10000 units of this drug following prosthetic valve replacement, platelets decreased persisted. Medication was switched to low-molecular-weight heparin. 1 day after discontinuation of readministration: To eliminate drug-induced thrombocytopenia, cefazolin sodium and famotidine were discontinued. 2 days after discontinuation of readministration: Since multiple cerebral infarction was confirmed in head CT and platelet count was $3.1 \times 10^4/mm^3$, HIT was suspected and medication was changed to argatroban. 3 days after discontinuation of readministration: Platelet count was $5.9 \times 10^4/mm^3$. 4 days after discontinuation of readministration: Platelet count recovered to $10.4 \times 10^4/mm^3$.	Company report
	Concomitant medications: dopamine hydrochloride, dobutamine hydrochloride, milrinone, nicardipine hydrochloride, insulin, famotidine, cefazolin sodium				

Clinical Laboratory Values

	2 days before administration	4 days after discontinuation (On day 1 of readministration)	On day 3 of readministration	On day 5 of readministration (day of discontinuation of readministration)	2 days after discontinuation of readministration	3 days after discontinuation of readministration	4 days after discontinuation of readministration
PLT ($\times 10^4$/mm^3)	16.4	1.3→0.8→11.0	1.1	6.4	3.1	5.9	10.4

PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 70s	Haemodialysis for chronic renal failure (cardiac failure, hypertension, diabetes mellitus)	8000 units (3 times a week) 32 days	**Heparin-induced thrombocytopenia (HIT)** Medication history of this drug: unknown On day 1 of administration: The patient was hospitalized due to cardiac failure and renal failure. Shunt was constructed for renal failure. Haemodialysis was performed 3 times a week. Afterwards, gradual decrease in platelets confirmed as shown in the table below. On day 32 of administration (day of discontinuation): Blood pressure decreased, chest pain developed immediately after starting dialysis. The patient developed acute myocardial infarction. Since HIT was suspected, administration of this drug was discontinued immediately. Medication was changed to 9.9 mL/hour of argatroban, acute myocardial infarction was treated conservatively. Antiheparin-PF4 complex antibody (HIT antibody) was positive in blood test. 1 day after discontinuation: From the day after discontinuation, medication was changed to 4 mL/hour of argatroban during dialysis. As a result of coronary angiography performed while using argatroban during chronic phase of myocardial infarction, 2 lesions, in the left anterior descending branch and the left circumflex branch were confirmed, it was decided to perform a PCI (percutaneous coronary intervention). After bolus administration of argatroban when starting PCI, it was possible to keep ACT (activated coagulation time) at approximately 300 seconds while continuing intravenous injection.	Company report
	Concomitant medications: doxazosin mesilate, efonidipine hydrochloride, warfarin potassium, orciprenaline sulfate, levothyroxine sodium, ursodeoxycholic acid, lansoprazole, teprenone				

Clinical Laboratory Values

	1 day before administration	On day 7 of administration	On day 30 of administration	On day 32 of administration (day of discontinuation)	Approx. 1 month after discontinuation
PLT ($\times 10^4$/mm^3)	17.7	14.7	16.3	10.0	18.2

PLT: Platelet

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Female 70s	Pulmonary thrombosis (heparin lock) (None)	40 units 13 days	**Heparin-induced thrombocytopenia (HIT)** The patient was hospitalized due to traffic accident. On day 1 of administration: Administration of heparin sodium (preparation with the indication for prevention of blood coagulation into indwelling intravenous route) was initiated. On day 9 of administration: Pulmonary thromboembolism developed and intravenous drip infusion of heparin sodium (10000 units/day) was initiated. On day 10 of administration: HIT developed. On day 13 of administration (day of discontinuation): Administration of this drug and heparin sodium discontinued. Anti-HIT antibodies measured → positive. 3.5 months after discontinuation: The symptom improved.	Company report
	Concomitant medications: none				

Clinical Laboratory Values

	On day 1 of administration	On day 2 of administration	On day 9 of administration	On day 10 of administration	5 days after discontinuation	21 days after discontinuation
PLT ($\times 10^4$/mm^3)	19.3	5.1	10.1	3.4	13.4	19.7
D-dimer (μg/mL)	241.75	93.60	114.00	98.20	57.10	6.07

PLT: Platelet

4 Triamcinolone Acetonide (injectable dosage form)

Brand Name (name of company)	Kenacort-A Intradermal Intraarticular (Bristol Pharmaceuticals Y.K.) Kenacort-A Intramuscular (Bristol Pharmaceuticals Y.K.)
Therapeutic Category	Adrenal hormone preparations
Indications	**Kenacort-A Intradermal Intraarticular** (Intraarticular injection) ○ Chronic rheumatoid arthritis, juvenile rheumatoid arthritis (including Still disease) ○ Acroarthritis (rheumatoid spondylitis) accompanying ankylosing spondylitis, osteoarthritis (when symptoms of inflammation are clearly confirmed), arthritis following injury, noninfectious chronic arthritis (Injection into soft tissue) ○ Periarthritis (limited to those that are noninfectious), tendonitis (limited to those that are noninfectious), peritendinitis (limited to those that are noninfectious) ○ Postoperative treatment after otorhinolaryngological surgery ○ Intractable stomatitis and glossitis (those that do not heal with local treatment) (Injection into tendon sheath) ○ Periarthritis (limited to those that are noninfectious), tendonitis (limited to those that are noninfectious), tendovaginitis (limited to those that are noninfectious), peritendinitis (limited to those that are noninfectious) (Intrasynovial injection) ○ Periarthritis (limited to those that are noninfectious), peritendinitis (limited to those that are noninfectious), synovial bursitis (limited to those that are noninfectious) (Localized intradermal injection)

	○ [Note]Eczema and dermatitis (acute eczema, subacute eczema, chronic eczema, contact dermatitis, eczema nummular, autosensitisation dermatitis, atopic dermatitis, infantile eczema, lichen simplex chronicus Vidal, other neurodermatitis, seborrheic dermatitis, progressive keratodermia tylodes palmaris progressiva, other dermatitis of the hand, genital or anal eczema, eczema or dermatitis of the auricle and external acoustic meatus, eczema or dermatitis of the nasal vestibule and ala of nose, etc.) (However, drug administration should be minimized to severe cases. Local injections should only be given when infiltration and lichenification are significant), [Note]Prurigo (including strophulus infantum, urticarial lichen, urticaria perstans) (limited to severe cases), [Note]psoriasis vulgaris from among psoriasis and similar cases [psoriasis vulgaris (severe cases), psoriatic arthropathy, psoriatic erythrodermia, pustular psoriasis, acrodermatitis continua, impetigo herpetiformis, Reiter syndrome], [Note]lichen planus (limited to severe cases), circumscribed scleroderma, [Note]alopecia areata (only for pernicious forms), [Note]early keloids and prevention of keloids ○ Postoperative treatment after otorhinolaryngological surgery (Nebulizer) ○ Bronchial asthma ○ Diffuse interstitial pneumonia (pulmonary fibrosis) (including radiation pneumonitis) ○ Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, laryngitis/oedema of the larynx, laryngeal polyp/knot, inflammation of the esophagus (corrosive oesophagitis, after use of directoscope) and after esophageal dilation procedure, postoperative treatment after otorhinolaryngological surgery (Intranasal injection) ○ Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, postoperative treatment after otorhinolaryngological surgery (Injection into the sinus) ○ Sinusitis/nasal polyps, postoperative treatment after otorhinolaryngological surgery (Laryngeal/tracheal injection) ○ Laryngitis/oedema of the larynx, laryngeal polyp/knot, postoperative treatment after otorhinolaryngological surgery (Injection into middle ear cavity) ○ Acute and chronic otitis media, exudative otitis media/stenosis of the auditory tube, postoperative treatment after otorhinolaryngological surgery (Injection into Auditory tube) ○ Exudative otitis media/stenosis of the auditory tube (Injection into turbinate) ○ Allergic rhinitis, pollinosis (hay fever), postoperative treatment after otorhinolaryngological surgery (Injection into nasal polyp) ○ Sinusitis/nasal polyps (Esophageal infusion) ○ Inflammation of the esophagus (corrosive oesophagitis, after use of directoscope) and after esophageal dilation procedure, postoperative treatment after otorhinolaryngological surgery Note: The drug should only be administered when the effect of external dosage form is insufficient or is expected to be insufficient. **Kenacort-A Intramuscular** (Intramuscular injection) ○ Chronic adrenal cortical insufficiency (primary, secondary, pituitary, iatrogenic), *adrenogenital syndrome, * subacute thyroiditis, *thyrotoxicosis [thyrotoxic (toxic) crisis] ○ Chronic rheumatoid arthritis, juvenile rheumatoid arthritis (including Still disease), rheumatic fever (including rheumatic carditis), polymyalgia rheumatica ○ Erythematosus (systemic and chronic discoid), systemic vasculitis (including

	aortitis syndrome, periarteritis nodosa, polyarteritis, Wegener's granulomatosis), polymyositis (dermatomyositis), *scleroderma ○ *Nephrosis and nephrotic syndrome ○ *Congestive heart failure ○ Bronchial asthma (limited to cases for which a route other than intramuscular injection is inappropriate), *Drugs and chemicals allergies and poisoning (including drug rash and toxicoderma), *serum sickness ○ *Serious infectious disease (used concomitantly with chemotherapy) ○ *Haemolytic anemia (those suspected of involving the immune system or immune mechanism), *leukemia (including acute leukemia, acute transformation of chronic myeloid leukemia, chronic lymphatic leukemia) (including leukemia cutis), *granulocytopenia (essential and secondary), *peliosis (thrombocytopenic purpura and nonthrombocytopenic purpura), *aplastic anaemia, *haemorrhagic diathesis due to hindrance by coagulation factors ○ *Regional enteritis, *ulcerative colitis ○ *General improvement of serious wasting disease (including terminal cancer and sprue) ○ *Cirrhosis (active, with accompanying intractable ascites, or accompanying cholestasia) ○ *Encephalomyelitis (including encephalitis and myelitis) (however, this drug should be used for a short period in the case of primary encephalitis when symptoms of increased intracranial pressure are observed and effect from other drugs is insufficient), *peripheral neuritis (including Guillain Barre syndrome), *myasthenia gravis, *multiple sclerosis (including optic myelitis), *chorea minor, *facial palsy, *spinal arachnoiditis ○ *Malignant lymphoma (lymphosarcomatosis, reticulosarcomatosis, Hodgkin disease, cutaneous reticulosis, mycosis fungoides) and similar diseases (closely related diseases), *eosinophilic granuloma ○ *Idiopathic hypoglycaemia ○ Adrenalectomy, *organ and tissue transplant, *surgical procedures for patients with adrenal cortical insufficiency ○ *Snake venom and insect poison (including serious insect bites) ○ Ankylosing spondylitis (rheumatoid spondylitis) ○ *Prevention of postoperative adhesions for salpingoplasty ○ *Prostate cancer (if other therapies are ineffective), *recurrent and metastatic breast cancer ○ Note Eczema and dermatitis (acute eczema, subacute eczema, chronic eczema, contact dermatitis, eczema nummular, autosensitisation dermatitis, atopic dermatitis, infantile eczema, lichen simplex chronicus Vidal, other neurodermatitis, seborrheic dermatitis, progressive keratodermia tylodes palmaris progressiva, other dermatitis of the hand, genital or anal eczema, eczema or dermatitis of the auricle and external acoustic meatus, eczema or dermatitis of the nasal vestibule and ala of nose, etc.) (However, drug administration should be minimized to severe cases.), *urticaria (except chronic cases) (limited to severe cases), Note *psoriasis and similar cases [psoriasis vulgaris (severe cases), psoriatic arthropathy, psoriatic erythrodermia, pustular psoriasis, acrodermatitis continua, impetigo herpetiformis, Reiter syndrome], Note *palmoplantar pustulosis (limited to severe cases), Note *lichen planus (limited to severe cases), *scleredema adultorum, *erythema (Note erythema multiforme exudativum, erythema nodosum) (however, limited to severe cases of erythema multiforme exudativum), *oculomucocutaneous syndrome [ectodermosis erosiva orificialis, Stevens-Johnson syndrome, dermatostomatitis, Fuchs syndrome, Behcet disease (provided there are no ocular conditions), Lipschutz' ulcer], pemphigus (pemphigus vulgaris, pemphigus foliaceous, Senear-Usher syndrome, pemphigus vegetans), * Duhring herpetiform dermatitis (including pemphigoid, herpes gestationis), *herpes zoster (limited to severe cases), Note *erythroderma (including pityriasis rubra Hebra) ○ Note *Prurigo (including strophulus infantum, urticarial lichen, urticaria perstans) (However, drug administration should be limited to severe cases. In addition, local injection is desirable for urticaria perstans)

	○ *Symptomatic treatment for inflammatory diseases of the inner eye, optic nerves, orbit, and eye muscle (uveitis, chorioretinitis, retinal vasculitis, optic neuritis, inflammatory pseudotumor of orbit, orbital apex syndrome, ophthalmoplegia), *when eye drops are unsuitable or insufficient as symptomatic treatment for inflammatory diseases of the outer and anterior region of the eye (blepharitis, conjunctivitis, keratitis, scleritis, iridocyclitis) ○ *Acute and chronic otitis media, *exudative otitis media/stenosis of the auditory tube, allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, laryngitis/oedema of the larynx, laryngeal polyp/knot, *inflammation of the esophagus (corrosive oesophagitis, after use of directoscope) and after esophageal dilation procedure, postoperative treatment after otorhinolaryngological surgery ○ Post-treatment after surgery by a dental surgeon (Intra-articular injection) ○ Chronic rheumatoid arthritis, juvenile rheumatoid arthritis (including Still disease) ○ Acroarthritis (rheumatoid spondylitis) accompanying ankylosing spondylitis, osteoarthritis (when symptoms of inflammation are clearly confirmed), arthritis following injury, noninfectious chronic arthritis (Injection into soft tissue) ○ Periarthritis (limited to those that are noninfectious), tendonitis (limited to those that are noninfectious), peritendinitis (limited to those that are noninfectious) ○ Postoperative treatment after otorhinolaryngological surgery ○ Intractable stomatitis and glossitis (those that do not heal with local treatment) (Injection into tendon sheath) ○ Periarthritis (limited to those that are noninfectious), tendonitis (limited to those that are noninfectious), tendovaginitis (limited to those that are noninfectious), peritendinitis (limited to those that are noninfectious) (Intrasynovial injection) ○ Periarthritis (limited to those that are noninfectious), peritendinitis (limited to those that are noninfectious), synovial bursitis (limited to those that are noninfectious) (Nebulizer) ○ Bronchial asthma ○ Diffuse interstitial pneumonia (pulmonary fibrosis) (including radiation pneumonitis) ○ Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, laryngitis/oedema of the larynx, laryngeal polyp/knot, inflammation of the esophagus (corrosive oesophagitis, after use of directoscope), and after esophageal dilation procedure, postoperative treatment after otorhinolaryngological surgery (Intranasal injection) ○ Allergic rhinitis, pollinosis (hay fever), sinusitis/nasal polyps, postoperative treatment after otorhinolaryngological surgery (Injection into the sinus) ○ Sinusitis/nasal polyps, postoperative treatment after otorhinolaryngological surgery (Laryngeal/tracheal injection) ○ Laryngitis/oedema of the larynx, laryngeal polyp/knot, postoperative treatment after otorhinolaryngological surgery (Injection into middle ear cavity) ○ Acute and chronic otitis media, exudative otitis media/stenosis of the auditory tube, postoperative treatment after otorhinolaryngological surgery (Injection into auditory tube) ○ Exudative otitis media/stenosis of the auditory tube (Injection into turbinate) ○ Allergic rhinitis, pollinosis (hay fever), postoperative treatment after otorhinolaryngological surgery

	(Injection into nasal polyp) ○ Sinusitis/nasal polyps (Esophageal infusion) ○ Inflammation of the esophagus (corrosive oesophagitis, after use of directoscope) and after esophageal dilation procedure, postoperative treatment after otorhinolaryngological surgery ＊ : When oral administration is not possible. Note : The drug should only be administered when the effect of external dosage form is insufficient or is expected to be insufficient.

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

[Important Precautions]

As the administration of adrenocortical hormone preparations including this drug may aggravate asthmatic attacks in patients with asthma bronchial. Particular cautions should be exercised when administering this drug to patients with asthma sensitive to drugs, foods, or additives etc.

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if symptoms such as dyspnoea, generalized flushing, vascular oedema, and urticaria are observed, discontinue administration and take appropriate measures.

Aggravation of asthmatic attacks: Sufficient cautions should be exercised as this drug may aggravate asthmatic attacks in patients with asthma bronchial.

Blindness, visual impairment: As it has been reported that blindness and visual impairment have occurred due to the development of retinal artery occlusion from injections into the head and neck area (scalp, intranasal injection, etc.). Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information>

Number of reported adverse reaction cases in about the last 3 years (April 2003 to January 2006) (events for which a causality to the drug could not be denied)

- Blindness, visual impairment: 1 case (no fatal case)
- Shock: 3 cases (no fatal case)

The number of patients treated with Triamcinolone for a year estimated by MAH: approximately 390000 (FY2005)

Marketed in Japan in: 1965

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	Subcutaneous scarring at left eyebrow (facial trauma)	2 mg Once	**Retinal artery occlusion** On day 1 of administration: The subcutaneous haematoma after traumatic injury under the skin of the left eyebrow had become an induration. After administering lidocaine hydrochloride/epinephrine as a subcutaneous local anesthetic, suction of the hematoma was tried using an 18G needle. As a scar-like hardness was confirmed with the end of the needle, 2 mg of this drug was injected into the induration. The patient complained of "left eye being blurry and difficult to see". Pupils were checked but there were no particular problems and the patient waited outside of the examination room.	Company report

				5 minutes after administration: The patient complained that “left eye is completely dark and it is impossible to see.” Based on the symptoms, retinal artery occlusion was suspected, and the patient received diagnosis and treatment at the department of ophthalmology. 2 hours and 20 minutes after administration: Visual acuity in right eye: 1.0, left eye: 0.09 (cannot be corrected), visual field defect (central area, including area with physiological scotoma). 2 hours and 35 minutes after administration: Eye massage was conducted. 2 hours and 40 minutes after administration: Sublingual nitroglycerin was performed. 3 hours after administration: Intravenous drip infusion of 300 mg of acetazolamide injectable dosage form and 200 mL of glycerin/fructose was conducted. Anterior chamber paracentesis was performed. The patient went home after receiving prescription for oral drugs. 1 day after administration: Visual acuity in left eye: 0.1 (cannot be corrected). 2 days after administration: Stellate ganglion block was performed at department of anesthesia. Visual acuity was improved after 3 minutes later upon opening eyelid. Left visual acuity improved to 0.9.	
	Concomitant medications: lidocaine hydrochloride/epinephrine				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 60s	Right rotator cuff tendinitis (right rotator cuff injury, fracture of the right distal radius)	20 mg Once	**Anaphylactic shock** On day 1 of administration: Injection into right shoulder joint (20 mg of this drug, 20 mg of mepivacaine hydrochloride) was performed. 30 minutes after administration: Sudden development of urticaria all over body. Itching became significant. 35 minutes after administration: Blood pressure was decreased to 80 mmHg range, oxygen saturation 88%, nausea developed. Temporary depressed level of consciousness was observed. Administration of oxygen and drip infusion were implemented, treatment for shock was conducted through injection of methylprednisolone sodium succinate, subcutaneous injection of epinephrine, etc. 58 minutes after administration: Blood pressure was recovered to 159/81 mmHg. Consciousness was lucid. For generalized management, the patient was hospitalized. Urticaria persisted at night, but it was disappearing. 1 day after administration: No particular decrease in blood pressure was observed, the condition was improved. Urticaria was also improved. 2 days after administration: Scratch tests (① 0.1-fold dilution of this drug, ② stock solution of this drug, ③ 1% mepivacaine hydrochloride) were performed. ① to ③ were negative both after 15 minutes and after 30 minutes. The patient was discharged from the hospital.	Company report
	Concomitant medications: mepivacaine hydrochloride				

5 Norcholestenol Iodomethyl (^{131}I)

Brand Name (name of company)	Adosterol-I 131 Injection (Daiichi Radioisotope Laboratories, Ltd.)
Therapeutic Category	Radioactive drugs
Indications	Local diagnosis of areas with adrenal gland disorder based on a scintigram of the adrenal gland.

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

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Anaphylactoid symptoms such as shock, angioedema, and dyspnoea may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures should be taken.

<Reference Information>

Number of reported adverse reaction cases in about the last 3 years (April 2003 to January 2006) (events for which a causality to the drug could not denied)
- Anaphylactoid symptoms: 1 case (of which 1 had a fatal case)

The number of patients treated with Norcholestenol for a year estimated by MAH: approximately 3000 (FY2005)
Marketed in Japan in: 1980

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Adrenal scintigraphy (hypertension, hyperlipidaemia, osteoporosis)	Approx. 15 MBq Once	**Anaphylactic shock** Primary disease: suspicion of renal carcinoma or adrenal carcinoma On day 1 of administration: This drug was diluted (37 MBq/4.8 mL) and slowly administered. 10 to 30 seconds after administration: Starting when 2 mL was administered, redness of face and dyspnoea developed. Afterwards, artificial respiration was initiated and epinephrine was administered. Thoracentesis was performed (pneumothorax was suggested by subcutaneous emphysema). Approx. 20 minutes after administration: Cardiac arrest, chest X-ray was conducted (mediastinal emphysema was confirmed later), cardiac compression was initiated, epinephrine and atropine sulfate were administered. Afterwards, catecholamine preparations were administered 8 times. Thoracostomy tube was inserted, 500 mg of methylprednisolone sodium succinate was administered. 30 minutes after administration: Pupils dilated. Approx. 1 hours after administration: Death was confirmed.	Company report
	Concomitant medications: olopatadine hydrochloride, sucralfate, codeine phosphate, magnesium oxide, dexamethasone, furosemide				

6 Mecobalamin/Folic Acid/d-α-Tocopherol Acetate/Fursultiamine Hydrochloride/Pyridoxine Hydrochloride

Brand Name (name of company)	Nabolin S (Eisai Co., Ltd.)
Therapeutic Category	Multivitamin preparations (over the counter drug)
Indications	Alleviation of the following symptoms: Neuralgia, myalgia/arthralgia (low back pain, shoulder muscle stiffness, frozen shoulder), numbness of the hands and feet, asthenopia

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

[When not to use the product]

This product should not be used in the following persons.
People who have had allergic symptoms in relation to this drug.

[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.
Shock (anaphylaxis): Immediately after administration, urticaria, oedema, chest distress, etc. may occur concurrently with pallor facial, cold hands and feet, cold sweat, and respiratory discomfort.

<Reference Information>

Number of reported adverse reaction cases between August 2003 (initial marketing in Japan) and January 2006 (events for which a causality to the drug could not be denied)
- Anaphylactoid symptoms: 5 case (no fatal case)

The number of patients treated with Mecobalamin, Folic Acid, Tocopherol, Fursultiamine, Pyridoxine for a year estimated by MAH: approximately 450000 (FY2005)
Marketed in Japan in: August 2003

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 40s	Back pain, musculoskeletal stiffness (none)	1 tablet 1 day	**Anaphylactoid reaction** On day 1 of administration: The patient took 1 tablet of this drug and 2 tablets of a chondroitin sulfate sodium drug (which the patient had taken previously but had not experienced adverse reactions) together for low back pain and shoulder muscle stiffness. Around 40 minutes after administration, itching and urticaria developed on the patient's body, abdominal pain and diarrhoea were confirmed, and dyspnoea was observed. Approximately 1 hour after administration, the patient made an outpatient visit and received consultation at hospital A. Dyspnoea, blood pressure decreased (90/58 mmHg), generalized rash were confirmed. The patient was treated through hydrocortisone sodium succinate injectable dosage form, *d*-chlorpheniramine maleate drip infusion, epinephrine, tranexamic acid drip infusion, and oral administration of *d*-chlorpheniramine maleate. Symptoms were improved.	Company report

				Blood pressure after hospitalization was 100/67 mmHg 2.5 hours after administration, 112/64 mmHg 4.6 hours after administration, 98/63 mmHg 5.2 hours after administration and 110/60 mmHg 10.2 hours after administration. 2 days after discontinuation: In the morning, blood pressure was 102/58 mmHg. As improvement in symptoms was confirmed, the patient was discharged from the hospital. 37 days after discontinuation: Prick test with this drug and chondroitin sulfate sodium drug was performed at hospital B. Welts (16 × 22 mm) were confirmed for this drug, and judged as being positive. The chondroitin sulfate sodium drug was negative. 57 days after discontinuation: Prick test performed once more for 5 main ingredients of this drug and the following additives: talc, carnauba wax, stearic acid, pullulan, povidone, and macrogol. Welts (8 × 16 mm) were confirmed for only folic acid, and judged as being positive.	
	Concomitant medications: chondroitin sulfate sodium drug				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 60s	Musculoskeletal stiffness, asthenopia (hypertension, hyperlipidaemia)	1 tablet 1 day	**Anaphylactoid symptoms** On day 1 of administration: The patient felt shoulder muscle stiffness and fatigue of the eyes, and took 1 tablet of this drug, which her family member was taking. Approximately 30 minutes after administration of this drug, itching and rash developed and the patient received consultation at this hospital. The patient started feeling sick in the waiting room. Loss of consciousness occured on the way to the toilet. Blood pressure found to be 80 mmHg by palpation. Skin eruption was confirmed. The patient made nearly full recovery through administration of vasopressor and adrenocortical steroid preparation.	Company report
	Concomitant medications: benazepril hydrochloride, pravastatin sodium				

3

Revision of PRECAUTIONS

(No. 175)

(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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 223) (excluding those presented in "2. Important Safety Information" of this Bulletin), together with reference materials.

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1 <Antispasmodics>
Piperidolate Hydrochloride

[Brand Name]	Dactil Tab. (Kissei Pharmaceutical Co., Ltd.) and other
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with significant elevations of AST (GOT) or ALT (GPT) and jaundice may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.
<Reference Information>	Company report

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2 <Vasoconstrictors>
Eletriptan Hydrobromide

[Brand Name]	Relpax Tablets 20 mg (Pfizer Japan Inc.)
[Adverse Reactions (clinically significant adverse reactions)]	**Epileptiform attacks:** Epileptiform attacks may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.
<Reference Information>	Company report

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3 <Vasodilators>
Isosorbide Dinitrate (transdermal patch)
Nitroglycerin (ointment, adhesive patch)

[Brand Name]	Frandol Tape S (Toa Eiyo Ltd.) and others Vasolator Oint. (Sanwa Kagaku Kenkyusho Co., Ltd.) Nitroderm TTS (Novartis Pharma K.K.) and others
[Precautions in Use]	It is recommended to give guidance to patients and family members, etc., to give consideration to the area for application so that automated external defibrillators (AEDs) are not obstructed.
<Reference Information>	Company report

4 <Bronchodilators> Salmeterol Xinafoate

[Brand Name]

Serevent 25 Rotadisk and 50 Rotadisk, Serevent 50 Diskus (GlaxoSmithKline K.K.)

[Important Precautions]

The fundamental for treatment of asthma bronchial is the use of anti-inflammatory agents such as inhaled steroid drugs; this drug should be used concomitantly with inhaled steroid drugs only in cases where improvements in symptoms are not obtained through inhaled steroid drugs, etc., or it is judged that treatment through concomitant use of inhaled steroid drugs, etc. is appropriate based on the severity of the patient.

As this drug is not an alternative agent for anti-inflammatory agents such as inhaled steroid drugs, cautions should be exercised for patients, caregivers, or appropriate people who serve as caregivers so that the patient does not reduce the dosage or discontinue taking inhaled steroid drugs without instruction from a physician and so that the patient does not take this drug only, even in cases where the patient feels improvements in symptoms through the use of this drug.

With regard to acute seizures that occur during the treatment with this drug, cautions should be exercised for patients, caregivers, or appropriate people who serve as caregivers so that other appropriate drugs such as short-acting inhaled beta-2 agonists are used.

Since it can be considered that asthma control is insufficient if the amount of such drugs increases or when there is not enough efficacy, cautions should be exercised for patients, caregivers, or appropriate people who serve as caregivers so that the patient receives a consultation and treatment from a medical institution as quickly as possible. In addition, if such kind of a condition is observed, it may be life-threatening, and reinforcement of anti-inflammatory therapy such as an increase in the amount of inhaled steroid drugs, should be carried out.

[Other Precautions]

As a result of the multicenter, placebo-controlled study conducted in the United States for 28 weeks in patients with asthma, there was no significant difference between the salmeterol (aerosol) arm and the placebo arm for the overall patient population in relation to the total number of deaths and life-threatening events relating to the respiratory tract, which was the primary endpoint. However, significant difference was observed in the salmeterol arm of the African-American patient population. The number of deaths relating to asthma, which was one of the secondary endpoints, was significantly higher in the salmeterol arm.

<Reference Information>

Nelson, H.S.,et al.: Chest 2006; 129: 15-26

5 <Oxytocics> Methylergometrine Maleate (oral dosage form)

[Brand Name]

Methergin Tablets (Novartis Pharma K.K.) and others

[Adverse Reactions (clinically significant adverse reactions)]

Anaphylactoid symptoms: Anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information>

Company report

6 <Oxytocics>
Methylergometrine Maleate (injectable dosage form)

[Brand Name] Metenarin Injection 0.2 (Aska Pharmaceutical Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored and if symptoms such as blood pressure decreased, nausea, vomiting, cyanosis, and dyspnoea are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

7 <Analgesics, anti-itchings, astringents, anti-inflammatory agents>
Diclofenac Sodium (dermatological)

[Brand Name] Naboal Gel, Naboal Tape (Hisamitsu Pharmaceutical Co., Inc.), Voltaren Gel, Voltaren Tape (Dojin Iyaku-Kako Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Contact dermatitis:** Dermatological symptoms such as redness, erythema, rash, itching, and pain may occur in the site of application and aggravate into swelling, oedema, blisters/erosions, etc., affect the whole body and become serious. If abnormalities are observed, discontinue administration immediately and take appropriate measures.

<Reference Information> Company report

8 <Epidermides-Miscellaneous>
Calcipotriol

[Brand Name] Dovonex Ointment (Teikoku Seiyaku Co., Ltd.)

[Important Precautions] This drug is an active-form vitamin D_3 preparation and may increase serum calcium level. Since hypercalcemia may induce a decrease in renal function, patients should be monitored for serum calcium level and renal function (e.g. creatinine and BUN) periodically (once at 2 - 4 weeks after the start of administration of the product and when deemed necessary thereafter). If any abnormality is observed in these values, the administration of the product should be discontinued until normal calcium levels are restored.
Overdosage of the product may induce hypercalcemia. Hypercalcemia may also occur in patients using the product for eruption covering a large area of the body or in patients with deteriorated skin barrier function which may accelerate percutaneous absorption of the drug. If any abnormality suggestive of hypercalcemia is observed, the administration of the product should be discontinued immediately and the patient should be followed up by monitoring biochemical parameters such as serum and urinary calcium levels.

[Adverse Reactions (clinically significant adverse reactions)] **Hypercalcemia**: Hypercalcemia and signs/symptoms considered to be due to hypercalcemia (malaise, weakness, anorexia, vomiting, abdominal pain, muscular weakness, etc.) may occur. If any abnormality is observed, the administration of the product should be discontinued, biochemical examination such as determination of serum and urinary calcium levels should be conducted, and measures such as fluid therapy should be taken when necessary.
Acute renal failure: Acute renal failure associated with increased serum calcium level may occur. If any abnormalities such as increases in serum creatinine and/or BUN are observed, treatment should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

(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 Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 223) (excluding those presented in "1. Handling of lancing devices (component adjacent to a needle is not disposable) for obtaining blood samples" of this Bulletin).

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1 Implantable cardiac pacemakers and implantable cardioverter defibrillators

(interactions with the so-called smart key systems*)

* So-called smart key system: System where locking/unlocking of door locks and turning engines on/off is possible without having to insert a key

[Important Precautions (precautions of household electrical appliances and environmental settings)]

With automobiles, etc. equipped with systems where locking/unlocking of door locks and turning engines on/off is possible without having to insert a key, the electromagnetic waves that are emitted from the antenna of such systems may temporarily inhibit the output from implantable cardiac pacemakers, etc. Therefore, patients should be instructed to take precautions regarding the following points.

If a patient with this implantable product gets into a vehicle that is equipped with such a system, the implanted site of this product should be at least 22 cm away from the antenna that is built into the vehicle.

Since when opening and closing the door, electromagnetic waves are temporarily emitted from the antenna, do not open and close the door more than necessary.

When the devices that communicates with the built-in antenna that is held by the driver (hereinafter referred to as "mobile device") is carried out or separated from the vehicle, there are some vehicles where electromagnetic waves are regularly emitted from the antenna. When a patient with this implantable product is riding in the vehicle, the mobile device should not be carried out of the vehicle.

As there are vehicles where electromagnetic waves are regularly emitted from the antenna even when the vehicle is parked, patients should avoid leaning against the vehicle, peering into the vehicle, or coming in very close proximity of the vehicle even when outside of the vehicle.

When getting into a vehicle owned by another person, confirm whether it is a vehicle equipped with such a system.

4

List of products subject to Early Post-marketing Phase Vigilance

(As of May 1, 2006)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Moxifloxacin Hydrochloride / Avelox Tablets 400 mg	Bayer Yakuhin, Ltd.	December 9, 2005
Finasteride / Propecia Tablets-0.2 mg and -1 mg	Banyu Pharmaceutical Co., Ltd.	December 14, 2005
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

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”