Pharmaceuticals and Medical Devices Safety Information

No. 234 March 2007

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, Japanese only).

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Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Office of Safety,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

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No. 234 March 2007

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

[Outline of Information]

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

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

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

1

Standardization of color coding scheme for injection needles etc.

1. Introduction

In order to standardize the color coding scheme for the external diameter of sterile injection needles, sterile indwelling needles for peripheral vessels, respiratory tract suction catheters etc. (hereafter referred to as "injection needles etc.") and that of catheters, Ministry of Health, Labour and Welfare (MHLW) has announced the Notification No. 112, dated on March 25, 2005, regarding "The list of designated controlled devices designated by the Minister of Health, Labour and Welfare" (hereafter referred to as "the Notification").

The statements concerning injection needles etc. in the Notification will come into effect as of April 1, 2007, and a transition will be made towards standardization of color-coded products. This report aims to disseminate the information of the background, outline of changes, and the transition period, to raise the awareness of the healthcare providers.

2. Background

In accordance with article 23, section 2, item 1 of the Pharmaceutical Affairs Law, injection needles etc. that are in conformity with the standards set by the Minister of Health, Labour and Welfare are allowed for manufacturing and marketing. Until now, however, nationally uniform color coding standards for the external diameter of catheters and injection needles etc. did not exist. Color codes were independently decided by the manufacturers and some products with identical specification were found to have different colors, depending on the manufacturers. This was not a favorable situation in terms of safety.

Therefore, uniform standards for the performance, quality, and the purpose of use of injection needles etc. were established in the Notification. For the establishment of the quality standards, including that of color coding, Japanese Industrial Standards (JIS) were applied and due consideration was paid to ensure consistency with the ISO Standards. In view of the domestic distribution conditions, these standards including the new color coding scheme will apply to products to be released from April 1, 2007.

3. Outline of the changes

(1) Injection needles etc. subject to changes

- Injection needles (disposable hypodermic needle, disposable intra-arterial injection needle, disposable injection needle, multi-purpose syringe with needle)
- Blood collection needles (disposable blood collection needle)
- Winged needles (disposable intravenous winged needle, disposable scalp vein winged needle)
- Indwelling needles for haemodialysis (disposable dialysis needle, disposable needle catheter for haemodialysis, indwelling needle for dialysis)
- Indwelling needles for peripheral vessels (sterile puncture needle with plastic cannula)
- Respiratory tract suction catheters (suction kit, bronchial suction catheter, sterile suction tube and catheter, tracheal suction catheter)

Moreover, products including the above (e.g. infusion sets, blood transfusion sets) are also subject to the changes.

· Infusion sets (infusion sets for the use with infusion pump, dual-purpose infusion sets for the use with gravity feed/infusion pump)
· Blood transfusion sets (blood transfusion sets for exchange blood transfusion, blood transfusion sets)

(2) Color code to be standardized

The color coding scheme for injection needles etc. stipulated in the Notification is as shown below. The color codes are in compliance with the corresponding Japanese Industrial Standards (JIS) or the ISO Standards.

Injection needles, infusion sets*, blood transfusion sets*, blood collection needles, winged needles, indwelling needles for haemodialysis		
External diameter of a needle		Color
mm	G	
0.3		yellow
0.33	29	red
0.36		blue-green
0.4	27	medium grey
0.45	26	brown
0.5	25	orange
0.55	24	medium purple
0.6	23	deep blue
0.7	22	black
0.8	21	deep green
0.9	20	yellow
1.1	19	cream
1.2	18	pink
1.4	17	red-violet
1.6	16	white
1.8	15	blue-grey
2.1	14	pale green
2.4		purple
2.7		pale blue
3		green-yellow
3.4		olive brown

Indwelling needles for peripheral vessels		
External diameter of a needle		Color
mm	G	
0.6	26	purple
0.7	24	yellow
0.8, 0.9	22	deep blue
1.0, 1.1	20	pink
1.2, 1.3	18	deep green
1.4, 1.5	17	white
1.6, 1.7, 1.8	16	grey
1.9, 2.0, 2.1, 2.2	14	orange
2.3, 2.4, 2.5	13	red
2.6, 2.7, 2.8	12	light blue
3.3, 3.4	10	pale brown

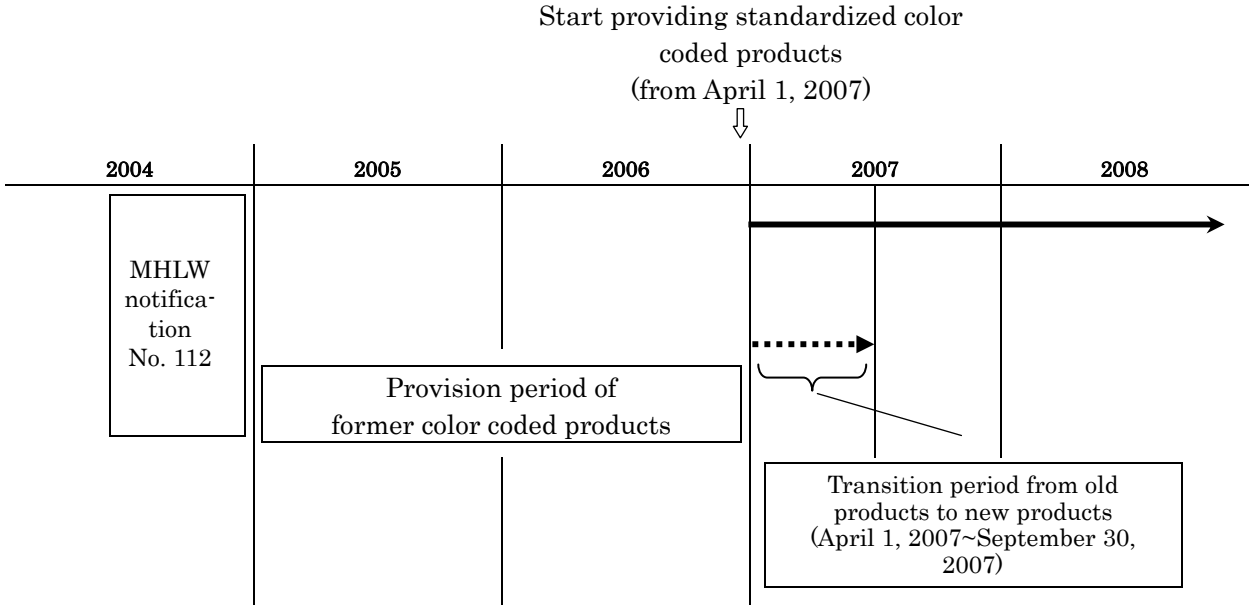
Respiratory tract suction catheters		
Catheter External diameter		Color
mm	Fr.	
1.67	5	grey
2.0	6	pale green
2.5	7.5	pink
2.67	8	pale blue
3.0	9	blue-green
3.33	10	black
4.0	12	white
4.67	14	green
5.0	15	brown
5.33	16	orange
6.0	18	red
6.67	20	yellow

* The changes will also be applicable to infusion sets and blood transfusion sets, etc. as the Japanese Industrial Standards (JIS) for both sets of equipment make reference to the JIS for injection needles etc.
* The color codes are based on the Japanese Industrial Standards (JIS) or ISO Standards.

(3) Transition period for the standardization of color coding scheme

Since the standards pertaining to injection needles etc. in the Notification will come into effect on April 1, 2007, the manufacturers of these injection needles will start the provision of standardized color coded products from April 1, 2007, and the replacement shall be completed within the six-month transition period, terminating on September 30, 2007. The marketing of injection needles etc. which are not compliant with the standardized color codes shall be prohibited after October 1, 2007, however, both old and new products will co-exist between April 1 and September 30, 2007.

Transition period



4. Request for healthcare providers

When using injection needles etc. in medical institutions, increased attention must be paid to avoid mix-ups of the color codes and the external diameter of needles and catheters. In particular, care will be needed if reference to the size of injection needles etc. is routinely made by their color codes (e.g. if 19 gauge injection needle is referred to as "the brown needle"). It may be necessary to change the method of identifying the size, for example, to specifying the "gauge" or "French". It is hoped that the standardization of color coding scheme for injection needles etc. is fully understood, and each medical institution to ensure thorough care and attention when handling these equipment.

5. Closing comments

More information on color coding can be found on the website of Japan Medical Devices Manufacturers Association (http://www.jmed.jp/) (in Japanese). For detailed information on the changes, please contact the manufacturers of the injection needles etc. that are being used in each medical institution.

Moreover, similar information can also be obtained from the "Medical Safety Information" section on the Pharmaceutical and Medical Devices Information website of the Pharmaceuticals and Medical Devices Agency (http://www.info.pmda.go.jp/).

2

Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated February 16, 2007.

1 Junchoto

Brand Name (name of Company)	TSUMURA Junchoto Extract Granules for Ethical Use (Tsumura & Co.) TAIKODO no Junchoto Extract Granules (Taikoseido Pharmaceuticals Co., Ltd.)
Therapeutic Category	Kampo medicines
Indications	Constipation

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

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia: If pyrexia, cough, dyspnoea, abnormal chest sound (crepitations), etc. occur, administration should be discontinued. Immediately perform a chest X-ray and undergo examinations, and appropriate measures such as administration of an adrenocortical hormone preparation should be taken. Patient should be instructed to discontinue administration and immediately contact a physician if pyrexia, cough, and dyspnoea, etc. occur.

<Reference Information>

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

- Interstitial pneumonia: 2 cases (no fatal case)

The number of patients treated with Junchoto for a year estimated by MAH (Marketing Authorisation Holder): approximately 21000 (2005)

Marketed in Japan in: 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Constipation (none)	7.5g Approximately 3 months	**Interstitial pneumonia** On day 1 of administration: Administration of this drug was started for constipation. Approx. on month 3 of administration: Dyspnoea on exertion appeared. Day of discontinuation: The patient received consultation at hospital A. Chest X-ray and CT revealed interstitial pneumonia, and hypoxemia was confirmed by blood gas test (PaO_2 67.6 torr in room air). At this point, the administration of this drug and butyric acid bacteria drug products was discontinued, and oral administration of clarithromycin (400 mg/day) was initiated. 7 days after discontinuation: Abnormal shadows were confirmed. Hypoxemia showed an improving tendency (PaO_2 78.5 torr in room air). 13 days after discontinuation: The patient was readmitted in hospital B for detailed examination. 42 days after discontinuation: As aggravation was not observed, the patient was discharged. There were no serological findings suggesting atypical pneumonia. Increase in total cell count and lymphocyte percentage, as well as decrease in CD 4/8 ratio were observed in bronchoalveolar lavage fluid.
	Concomitant medications: butyric acid bacteria drug products, magnesium oxide, sennoside, disopyramide, verapamil hydrochloride, sodium azulene sulfonate/L-glutamine, ubidecarenone, tandospirone citrate			

Clinical Laboratory Values

	Approx. 3 months after discontinuation (day of discontinuation)	7 day after discontinuation	14 days after discontinuation	140 days after discontinuation
WBC (/mm^3)	6400	7200	6300	5300
LDH (IU/L)	484	466	--	347
CRP (mg/dL)	1.4	--	--	--
KL-6 (U/mL)	1804	--	1740	490

WBC: White Blood Cell LDH: Lactate Dehydrogenase
CRP: C-Reactive Protein

Blood gas

	Approx. 3 months after administration (day of discontinuation)	7 day after discontinuation	13 days after discontinuation	140 days after discontinuation
pH	7.493	7.470	7.450	7.443
PaO_2 (torr)	67.6	78.5	88.6	97.6
$PaCO_2$ (torr)	34.7	36.9	37.6	36.0

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

Immune serum test

	Approx. 3 months after administration (day of discontinuation)
RA test	(–)
Anti-DNA antibodies	(–)

RA: Rheumatoid Arthritis

DLST

	17 days after discontinuation
Junchoto	(–) (in blood), (+) (in BALF)
Butyric acid bacteria drug products	(+) (in blood), (+) (in BALF)

Findings from BALF

	17 days after discontinuation
Total cell count ($\times 10^5$/mL)	8.4
Macrophage (%)	65.4
Lymphocytes (%)	33.8
Neutrophils (%)	0.4
Eosinophils (%)	0.3
CD 4/8 ratio	0.24

2 Seihaito

Brand Name (name of company)	TSUMURA Seihaito Extract Granules for Ethical Use (Tsumura & Co.)
Therapeutic Category	Kampo medicines
Indications	Cough, producing a large amount of sputum

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder with significant increase in AST (GOT), ALT (GPT), Al-P or γ-GTP etc. and jaundice may occur. Patient should be carefully monitored. If abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 2003 to January 2007) (events for which a causality to the drug could not be denied)

- Hepatic function disorder, jaundice: 2 cases (no fatal case)

The number of patients treated with Seihaito for a year estimated by MAH: approximately 24000 (2005)
Marketed in Japan in: 1986

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Bronchitis chronic (cholelithiasis, hyperlipidaemia)	9.0 g 69 days	**Hepatic function disorder** On day 1 of administration: Administration of this drug was started for bronchitis chronic. On day 61 of administration: Appetite impaired manifested. On day 63 of administration: The patient made an emergency room visit. She was hospitalized due to hepatic function disorder. On day 69 of administration (day of discontinuation): Administration of this drug was discontinued. 3 days after discontinuation: Administration of ursodeoxycholic acid at 600 mg/day was started. Hepatic function was gradually recovered. 17 days after discontinuation: The patient was discharged. 30 days after discontinuation: Administration of ursodeoxycholic acid was discontinued.
	Concomitant medications: theophylline, fudosteine, clarithromycin, ketotifen fumarate, pravastatin sodium			

Clinical Laboratory Values

	On day 63 day of administration	2 days after discontinuation	15 days after discontinuation	30 days after discontinuation
AST (GOT) (IU/L)	1301	1230	104	22
ALT (GPT) (IU/L)	1679	1263	181	23
Al-P (IU/L)	1337	1118	614	372
γ-GTP (IU/L)	605	542	202	90
LDH (IU/L)	--	457	194	182
Total bilirubin (mg/dL)	2.8	6.2	1.9	1.3
Direct bilirubin (mg/dL)	--	4.0	1.1	0.5

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

Virus marker

	On day 64 of administration
HA antibody (IgM)	(–)
HBs antigen	(–)
HBs antibody	(–)
HCV antibody	(–)
CMV antibody (IgM)	(–)
CMV antibody (IgG)	(+)
EBV-VCA	(+)
EBV-EBNA	(+)

HA: Hepatitis-A Virus
HBs: Hepatitis Virus Bs
HCV: Hepatitis C Virus
CMV: Cytomegalovirus
EBV-VCA: Epstein-Barr Virus, Viral Capsid Antigen
EBV-EBNA: Epstein-Barr Virus, Nuclear Antigen

Immune serum test

	On day 64 of administration
Antinuclear antibody	(–)
Antimitochondrial antibody (AMA)	(–)

DLST

	15 days after discontinuation
Seihaito	Positive (S.I.: 9.3)

Liver biopsy

2 days after discontinuation
High possibility of necrosis hepatocellular, hepatocellular injury type drug-induced liver disorder

3 Lansoprazole, Lansoprazole/Amoxicillin/Clarithromycin

❶ Lansoprazole

Brand Name (name of company)	Stanzome Capsules 15 and 30 (Shiono Chemical Co., Ltd.) Taiproton Capsules 15 mg and 30 mg (Taisho Pharmaceutical Industries, Ltd.) Takepron Capsules 15 and 30, Takepron OD Tablets 15 and 30, Takepron Intravenous 30 mg (Takeda Pharmaceutical Company Limited) Tapizol Capsules 15 and 30 (Taiyo Yakuhin Co., Ltd.) Lasopran Capsules 15 mg and 30 mg (Sawai Pharmaceutical Co., Ltd.) Laprazol Capsules 15 mg and 30 mg (Towa Pharmaceutical Co., Ltd.) Lansoprazole Capsules 15 mg and 30 mg "MED" (Medisa Shinyaku Inc.) Lansoprazole Capsules 15 mg and 30 mg "AMEL" (Kyowa Pharmaceutical Industry Co., Ltd.) Lansoral capsule 15 and 30 (Nichi-iko Pharmaceutical Co., Ltd.)
Therapeutic Category	Peptic ulcer agents
Indications	(oral administration) Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux oesophagitis, Syndrome Zollinger Ellison, non-erosive reflux disease (Takepron Capsules 15, Takepron

	OD Tablets 15 only), adjunct to *Helicobacter pylori* eradication in the case of gastric ulcer or duodenal ulcer (Takepron Capsules 15 and 30, Takepron OD Tablets 15 and 30 only) (injection) Following disorders for which oral administration is impossible Stomach ulcer with haemorrhage, duodenal ulcer, acute stress ulcer and acute gastric mucosal lesion

❷ Lansoprazole/Amoxicillin/Clarithromycin

Brand Name (name of company)	Lansap 400 and 800 (Takeda Pharmaceutical Company Limited)
Therapeutic Category	Antibiotics-Miscellaneous
Indications	<Susceptible strains> Amoxicillin and clarithromycin susceptible helicobacter pylori <Indications> Helicobacter pylori infectious disease in gastric ulcers/duodenal ulcers

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

[Adverse Reactions (clinically significant adverse reactions)]

Nephritis interstitial leading to acute renal failure may occur, caution should be exercised with respect to renal function tests (BUN, creatinine increase etc.). If abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

<Reference Information>

Regarding ❶❷

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

- Nephritis interstitial: 5 cases (no fatal case)

The number of patients treated with Lansoprazole and Lansoprazole/Amoxicillin/Clarithromycin for a year estimated by MAH: approximately 6.5 million (2006)

Marketed in Japan in: For ❶, December 1992
For ❷, December 2002

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Haemorrhage from carcinomatous ulcer caused by gastric cancer (diabetes mellitus, gastric cancer)	30 mg 8 days	**Acute renal failure** Medical history: none On day 1 of administration: The patient was receiving ambulatory care for diabetes mellitus at nearby physician, when epigastric ache occurred. Upper endoscopy revealed an extensive gastric ulcer haemorrhage due to gastric cancer in gastric antrum, therefore, hospitalization therapy was started on the same day. Administration of the drug was started. On day 2 of administration: Oliguria and renal function aggravated were observed. On day 8 of administration (day of discontinuation): Anuria was developed and advanced renal impairment was confirmed by a blood test. Therefore, the patient was diagnosed with acute renal failure. He was transferred to another hospital therapy was given. Generalized oedema (face oedema, oedema lower limb), pleural effusion and ascites were confirmed. After the administration on this day, the administration of this drug was discontinued. 1 day after discontinuation: Whole body control, including haemodialysis, lead to gradual recovery of renal function. Urination was gradually achieved, after changing the drug to H_2 blocker from this drug. However, adenocarcinoma was detected from the gastric lesion and the haemorrhage and pain from carcinomatous ulcer were aggravated. Administration of omeprazole resulted in oliguria again. The patient was therefore diagnosed with drug-induced renal failure acute due to PPI. Administration of the drug was discontinued. Argon laser was used for haemostasis, and strong analgesic was administered. 16 days after discontinuation: Haemodialysis was terminated. Tendency to improve in acute renal failure, anuria, generalized oedema, blood pressure increased, BUN, creatinine was observed. Renal biopsy (testing date unclear): Acute nephritis interstitial was confirmed.
	Concomitant medications: pioglitazone hydrochloride, glimepiride, brotizolam			

Clinical Laboratory Values

	26 days before administration	On day 8 of administration (day of discontinuation)	8 days after discontinuation	16 days after discontinuation	69 days after discontinuation
BUN (mg/dL)	17.2	53.9	109.8	58.4	15.7
Creatinine (mg/dL)	0.73	7.0	15.6	7.0	1.1
Urate	--	9.7	11.2	6.5	7.3
Urinary occult blood	--	(1+)	(3+)	--	(–)
Urinary protein	--	(3+)	(3+)	--	(–)
CRP (mg/dL)	--	1.30	--	--	5.99

BUN: Blood Urea Nitrogen CRP: C-Reactive Protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Gastric ulcer [A_2 stage] (hypertension, Bell's palsy)	30 mg 20 days	**Tubulointerstitial nephritis** Medical history: drug-induced skin eruption, appendicitis On day 1 of administration: Upper gastrointestinal tract endoscopy was conducted for epigastric ache. As the patient was diagnosed with gastric ulcer (A_2 stage), the administration of the drug was initiated. On day 20 of administration (day of discontinuation): The administration of the drug was discontinued, and was changed to sodium rabeprazole from the next day. 3 days after discontinuation: Malaise developed and renal failure acute (renal origin) was observed. The patient was hospitalized. 4 days after discontinuation: The administration of sodium rabeprazole was discontinued. 5 days after discontinuation: FENa was 2.5 % 6 days after discontinuation: The patient started to undergo haemodialysis (3 days/week) for renal failure acute. 8 days after discontinuation: Rheumatoid factors, ASO (antistreptolysin O antibodies) and ASK (antistreptokinase antibodies) were all negative. 10 days after discontinuation: MPO-ANCA was less than 10. PR3-ANCA was less than 10, anti-platelet antibodies (−). 17 days after discontinuation: Steroid therapy (prednisolone 30 mg/day) was started. 18 days after discontinuation: Renal biopsy was conducted. The test result confirmed tubulointerstitial nephritis. Renal biopsy: # Tubulointerstitial nephritis, most likely # hyaline arteriolosclerosis (nephrosclerosis), susp. DLST: sodium rabeprazole (negative) 22 days after discontinuation: As the patient showed signs of recovery, haemodialysis was temporarily terminated and a follow-up observation was conducted. 32 days after discontinuation: Haemodialysis was resumed. 38 days after discontinuation: As urine volume was maintained again, complete termination of haemodialysis was attempted. 41 days after discontinuation: Urine volume could be maintained. 45 days after discontinuation: Prednisolone was decreased (20 mg/day). 50 days after discontinuation: Renal impairment was remaining with serum creatinine level 3.04 mg/dL. 66 days after discontinuation: Prednisolone was decreased (5 mg/day). Renal function was slowly recovered, and it was decided to continue the treatment in another hospital. Serum creatinine at 2 mg/dL level (date of measurement unclear).

				88 days after discontinuation: The patient recovered.
	Concomitant medications: none			

Clinical Laboratory Values

	On day 2 of administration	1 day after discontinuation	3 days after discontinuation	4 days after discontinuation	8 days after discontinuation	18 days after discontinuation	50 days after discontinuation
BUN (mg/dL)	19.9	18.8	30.4	44.2	69.1	37.7	43.7
Creatinine (mg/dL)	1.04	0.95	2.50	4.63	10.14	6.01	3.04
Urate	--	--	--	7.85	8.06	4.70	6.64
Urinary protein	--	(+/–)	(3+)	--	(3+)	(1+)	(1+)
Urinary occult blood	--	(+/–)	(+/–)	--	(2+)	(+/–)	(–)
CRP (mg/dL)	0.87	0.63	--	4.38	7.57	0.92	0.06

BUN: Blood Urea Nitrogen CRP: C-Reactive Protein

3

Revision of PRECAUTIONS
(No. 185)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated February 16, 2007 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 <Central nervous system agents-Miscellaneous> Donepezil Hydrochloride

[Brand Name]

Aricept Fine Granules 0.5 %, Aricept Tablets 3 mg and 5 mg, Aricept D Tablets 3 mg and 5 mg (Eisai Co., Ltd.)

[Important Precautions]

Bradycardia, heart block (Sinoatrial block or atrioventricular block) and QT prolongation, etc. may occur after administering this drug. In particular, patients with cardiac disorders (myocardial infarction, valvular disorder and cardiomyopathy and others) and/or with electrolyte abnormalities (hypokalemia, etc.), should be carefully observed to prevent serious arrhythmia developing.

[Adverse Reactions (clinically significant adverse reactions)]

Syncope, bradycardia, heart block, QT prolongation, myocardial infarction and heart failure: Syncope, bradycardia, heart block (sinoatrial block or atrioventricular block), QT prolongation, myocardial infarction or heart failure may occur. In the event of such symptoms, appropriate measures, such as discontinuation of this drug, should be taken.

2 <Antispasmodics> Baclofen (oral dosage form)

[Brand Name]

Gabalon Tablets 5 mg and 10 mg (Daiichi Pharmaceutical Co., Ltd.), Lioresal Tablets 5 mg and 10 mg (Novartis Pharma K.K.)

[Precautions of Dosage and Administration]

As majority of this drug is excreted in the urine as the unchanged drug, blood concentration may increase in patients with decreased renal function. Therefore, administration of this drug should be initiated at a low dosage for patients with such condition. For patients with severe renal impairment and need to receive dialysis, precaution should be taken when administratinf this drug, such as initiating treatment, from 5 mg/day.

[Careful Administration]

Patient with decreased renal function. (As majority of Baclofen is excreted in the urine as unchanged drug, blood concentration may increase in such patients. Therefore, caution should be taken in the adjustment of the dosage. In particular, caution should be exercised to the symptoms of overdosage (consciousness disturbed, respiratory depression etc.) in patients with severe renal impairment and need to receive dialysis.

[Adverse Reactions (clinically significant adverse reactions)]

Consciousness disturbed, respiratory depression: Consciousness disturbed, respiration depressed and other symptoms of central nervous system suppression may occur. If abnormalities are observed, administration should be discontinued, and appropriate measures should be taken. These symptoms are more likely to develop in patients with renal function disorder, caution should be exercised.

3 <Hemostatics> Polidocanol (esophageal varices stiffening agent)

[Brand Name] Aethoxysklerol 1% Injection (Sakai Chemical Industry Co., Ltd.)

[Contraindications] Patients with a history of hypersensitivity to any components of this product

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur. Patient should be carefully monitored from the initiation of administration. If wheezing, dyspnoea, blood pressure decreased, loss of consciousness, generalised flushing, urticaria, angioedema (such as face oedema and laryngeal oedema) etc. are observed, administration should be discontinued and appropriate measures should be taken.

4 <Antineoplastics-Miscellaneous> Fadrozole Hydrochloride Hydrate

[Brand Name] Afema Tab. 1 mg (Novartis Pharma K.K.)

[Important Precautions] Osteoporosis and bone fracture may occur more frequently due to the administration of this drug. It is recommended to conduct periodic check-up of bone conditions, including bone density.

5 <Antineoplastics-Miscellaneous> Letrozole

[Brand Name] Femara Tablets 2.5 mg (Novartis Pharma K.K.)

[Important Precautions] Osteoporosis and bone fracture may occur more frequently due to the administration of this drug. It is recommended to conduct periodic check-up of bone conditions, including bone density.

6 <Antivirals> Ribavirin

[Brand Name] Rebetol Capsules 200 mg (Schering-Plough K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Haemorrhage of digestive tract (melaena, bloody stool), peptic ulcer, small intestine ulcer, colitis ischaemic: Patient should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP): Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), with platelets decreased, anaemia and renal failure as major symptoms, may occur. Patient should be carefully monitored through periodic blood test (platelet count, red blood cell count etc.) and renal function test. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Biological preparations-Miscellaneous>

7 Interferon Alfa-2b (Genetical recombination)

[Brand Name] Intron A Sterile Powder for Injection 300, 600, and 1000 (Schering-Plough K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP): Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), with platelets decreased, anaemia and renal failure as major symptoms, may occur. Patient should be carefully monitored through periodic blood test (platelet count, red blood cell count etc.) and renal function test. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Biological preparations-Miscellaneous>

8 Peginterferon Alfa-2b (Genetical recombination)

[Brand Name] PegIntron Sterile Powder for Injection 50 μg/0.5 mL, 100 μg/0.5 mL, and 150 μg/0.5 mL (Schering-Plough K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Thrombotic thrombocytopenic purpura (TTP): Thrombotic thrombocytopenic purpura (TTP), with platelets decreased, anaemia and renal failure as major symptoms, may occur. Patient should be carefully monitored through periodic blood test (platelet count, red blood cell count etc.). If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Over the counter drugs

9 Junchoto

[Brand Name] Junchoto Extract Granules KM (Kahya Co., Ltd.), Kampo Medicine Junchoto (Taikoseido Pharmaceuticals Co., Ltd.) and others

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

If the following symptoms are observed after taking this drug

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

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

Over the counter drugs

10 Seihaito

[Brand Name] Shoukakutenyo (extract granules) (Tatebayashi Shoukakudou), TOCHIMOTO no Seihaito (TOCHIMOTO TENKAIDO Co., Ltd) and others

[Cousultation] 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 a case.

Hepatic function disorder: 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

(As of March 1, 2007)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Alendronate Sodium Hydrate / Fosamac Tablets 35 mg	Banyu Pharmaceutical Co., Ltd.	September 15, 2006
Alendronate Sodium Hydrate / Bonalon Tablet 35 mg	Teijin Pharma Limited	September 15, 2006
Itraconazole / Itrizole Oral Solution 1%	Janssen Pharmaceutical K.K.	September 15, 2006
Temozolomide / Temodal Capsules 20 mg and 100 mg	Schering-Plough K.K.	September 15, 2006
Budesonide / Pulmicort Respules 0.25 mg and 0.5 mg	AstraZeneca K.K.	September 15, 2006
Entecavir Hydrate / Baraclude Tablets 0.5 mg	Bristol Myers K.K.	September 21, 2006
Cetrorelix Acetate / Cetrotide for Injection 0.25 mg and 3 mg	Nippon Kayaku Co., Ltd.	September 21, 2006
Manganese Chloride Tetrahydrate / Bothdel Oral Solution 10	Meiji Dairies Corporation	September 25, 2006
Gabapentin / Gabapen Tablets 200 mg, 300 mg, and 400 mg	Pfizer Japan Inc.	September 25, 2006
Olopatadine Hydrochloride / Patanol Ophthalmic Solution 0.1%	Alcon Japan Ltd.	October 5, 2006
Busulfan / Busulfex Injection 60 mg	Kirin Brewery Company, Limited	October 10, 2006[*1] / October 20, 2006[*2]
Fexofenadine Hydrochloride / Allegra Tablets 60 mg[*3]	Sanofi-Aventis K.K.	October 20, 2006
Landiolol Hydrochloride / Onoact 50 for Injection[*4]	Ono Pharmaceutical Co., Ltd.	October 20, 2006
Mozavaptan Hydrochloride / Physuline Tablets 30 mg	Otsuka Pharmaceutical Co., Ltd.	October 24, 2006
Interferon Beta-1a (Genetical recombination) / Avonex IM Injection Syringe 30 μg	Biogen Idec Japan Ltd.	November 6, 2006
Moxifloxacin Hydrochloride / Vegamox Ophthalmic Solution 0.5%	Alcon Japan Ltd.	November 6, 2006
Pneumococcal Vaccine / Pneumovax NP	Banyu Pharmaceutical Co., Ltd.	November 29, 2006

Bortezomib Velcade Injection 3 mg	Janssen Pharmaceutical K.K.	December 1, 2006
Itraconazole Itrizole Injection 1%	Janssen Pharmaceutical K.K.	December 6, 2006
Ropinirole Hydrochloride ReQuip Tablets 0.25 mg, 1 mg, and 2 mg	GlaxoSmithKline K.K.	December 6, 2006
Lansoprazole Takepron Intravenous 30 mg	Takeda Pharmaceutical Company Limited	December 7, 2006
Losartan Potassium/Hydrochlorothiazide Preminent Tablets	Banyu Pharmaceutical Co., Ltd.	December 8, 2006
Polidocanol Polidocasklerol 0.5%, 1%, and 3% Inj. 2 mL	Sakai Chemical Industry Co., Ltd.	December 14, 2006
Fexofenadine Hydrochloride Allegra Tablets 30 mg	Sanofi-Aventis K.K.	January 9, 2007
Perflubutane Sonazoid for Injection	Daiichi Pharmaceutical Co., Ltd.	January 10, 2007
Pemetrexed Sodium Hydrate Alimta Injection 500 mg	Eli Lilly Japan K.K.	January 22, 2007
Remifentanil Hydrochloride Ultiva Intravenous 2 mg and 5 mg	Janssen Pharmaceutical K.K.	January 22, 2007
Infliximab (Genetical recombination) Remicade for I.V. Infusion 100[*5]	Tanabe Seiyaku Co., Ltd.	January 26, 2007
Zanamivir Hydrate Relenza[*6]	GlaxoSmithKline K.K.	January 26, 2007
Tacrolimus Hydrate Prograf Capsules 0.5 mg and 1 mg[*7]	Astellas Pharma Inc.	January 26, 2007
Baclofen Intrathecal Gabalon 0.005%, 0.05%, and 0.2%[*8]	Daiichi Pharmaceutical Co., Ltd.	January 26, 2007
Micafungin Sodium Funguard 25 mg, 50 mg, and 75 mg for Infusion[*9]	Astellas Pharma Inc.	January 26, 2007
Rurioctocog Alfa (Genetical recombination) Advate Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method 250, 500, and 1000	Baxter Limited	Feburary 22, 2007

*1: For the adult dose initially approved
*2: An additional administration for “pediatrics”
*3: An additional administration for “pediatrics (aged 7 and older)”
*4: An additional indication for “emergency measures against following tachycardiac arrhythmia occurring under post-operative monitoring of circulatory dynamics: atrial fibrillation, atrial flutter, sinus tachycardia”
*5: An additional indication for “the treatment of refractory uveitis in patients with Behcet’s disease (only in cases which are not adequately responsive to conventional therapies)”
*6: An additional indication for “prophylaxis of influenza A or B virus infection”
*7: An additional indication for “Lupus nephritis (in a case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions)”
*8: Additional administration for “pediatrics”
*9: An additional indication for “Prophylaxis of Aspergillus and Candida infections in patients undergoing hematopoietic stem cell transplantation”

Reference Material

To all healthcare providers involved in the treatment of influenza
(precautionary statement regarding measures to be taken after the initiation of influenza treatment)

MHLW requested to the concerned organization to disseminate the following information (attachment) on the above-mentioned subject and instructed to the marketing authorisation holders to provide the same information to the healthcare providers.

(attachment)

February 28, 2007
Ministry of Health, Labour and Welfare

To all healthcare providers involved in the treatment of influenza
(reminder: measures to be taken after the initiation of influenza treatment)

○ This month, 2 tragic cases have been reported in the media where 2 junior high school students, who were thought to have taken oseltamivir phosphate (brand name: Tamiflu), an antiviral drugs for influenza virus, fell from their apartments and died. Further information on these 2 cases is currently being collected and experts will be called upon to carry out thorough studies, including the possible association with Tamiflu.

○ The association between the use of Tamiflu and psychological/neurological manifestations has been investigated and studied by the experts, as indicated in 2 and 3 of the attachment [Reference]. The results of these studies suggest that the association between the use of Tamiflu and the death, that is believed to be attributable to psychological/neurological symptoms, is unlikely. Therefore, at this stage, we do not think there is a serious safety concern regarding Tamiflu. However, in this season, further studies are being conducted to enable a more detailed review.

○ Although the association between Tamiflu and the death is thought to be unlikely at this stage under the aforementioned circumstance, abnormal behaviours of the patients infected with influenza virus have been reported in the past, prior to the initial marketing of Tamiflu, as shown in 4 of the attachment [Reference]. In rare cases, encephalitis/encephalopathy have also been reported to develop. Therefore, you are kindly requested to take due consideration of the precautions described below.

As preventive measures to avoid any possible accidents during recuperation at home, especially for children/minors, once the patient is diagnosed with influenza and the treatment is initiated with or without the prescription of Tamiflu, it will be appropriate;

① to explain that abnormal behaviour may occur

② caregivers should be careful not to let patients who are children/minors alone at least 2 days if they are treated at home.

Therefore, healthcare providers involved in the treatment of influenza are requested to provide appropriate explanation to the patients and family members.

Attachment

[References]

1 Although the causality between Tamiflu and “psychological/neurological symptoms” is unclear, on May 2004, the following sentence was added under the section “Clinically significant adverse reactions” in the package insert, in order to alert the medical and pharmaceutical providers: ”Psychoneurological symptoms (e.g. disturbances in consciousness, abnormal behaviour, delirium, hallucination, delusion, convulsions) may occur. If any abnormality is observed, the administration should be discontinued. Patients should be carefully monitored and appropriate therapeutic measures should be taken according to individual symptoms”. At the same time, the marketing authorisation holder (Chugai Pharmaceutical Co., Ltd.) was instructed to provide information to medical and pharmaceutical providers, including doctors and pharmacists.

2 By the end of 2006, 16 cases of deaths of children aged 16 and younger who took Tamiflu (including 1 case during clinical trial) have been reported, including that caused by abnormal behaviour. However, based on the discussions in Subcommittee on Drug Safety, Committee on Drug Safety of Pharmaceutical Affairs and Food Sanitation Council and hearings with the specialists of paediatrics, respiratory diseases etc., the causality between these events and the use of Tamiflu is seemed to be unlikely.

《Fiscal Year 2005, First Meeting of Subcommittee on Drug Safety, Committee on Drug Safety of Pharmaceutical Affairs and Food Sanitation Council (held on January 27, 2006) Reference material 4-4》
http://www.mhlw.go.jp/shingi/2006/01/dl/s0127-9d04.pdf (in Japanese)

3 According to “The research on the manifestation of influenza-associated symptoms” supported by grant from Ministry of Health, Labour and Welfare for FY2005 (Principal Investigator: Shunpei Yokota (Professor of the Department of Child Health and Development, Yokohama City University School of Medicine), in which a study of approximately 2800 children was conducted to compare the occurrence of abnormal behaviour, statistically significant difference was not found between the groups with Tamiflu and without Tamiflu. (This research is also conducted in this season for more detailed investigation)

《Ministry of Health, Labour and Welfare Grants, Research Report of Fiscal Year 2005, “The research on the manifestation of influenza-associated symptoms”》
http://www.mhlw.go.jp/topics/2006/10/dl/tp1020-2.pdf (in Japanese)

4 Furthermore, a survey on the actual situation of encephalitis/encephalopathy occurring during clinical course of influenza had been conducted by the Ministry of Health and Welfare (at the time) between January and March 1999, before the date of initial marketing of Tamiflu (February, 2001). In this report, descriptions of psychological/neurological symptoms such as consciousness disturbed, convulsions, abnormal behaviour etc. as the conditions and the course of encephalitis/encephalopathy can be found.

《”Occurrence of encephalitis/encephalopathy during the clinical course of influenza” dated June 25, 1999》
http://www1.mhlw.go.jp/houdou/1106/h0625-2_11.html (in Japanese)