Pharmaceuticals and Medical Devices Safety Information

No. 211 March 2005

Table of Contents

1. **Important Safety Information** 2

1 Raloxifene Hydrochloride 2
2 Quetiapine Fumarate 3
3 Blood Glucose Self-monitoring Kit (those using the glucose dehydrogenase method and coenzyme pyroloquinoline quinone) 6

2. **Revision of PRECAUTIONS (No. 164)**
Trandolapril (and 4 others) 8

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

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

This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

1

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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 210), together with reference materials.

1 Raloxifene Hydrochloride

Brand Name (name of company)	Evista Tablets 60 mg (Eli Lilly Japan K.K.)
Therapeutic Category	Miscellaneous metabolism agents
Indications	Osteoporosis in postmenopausal women

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

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder: Hepatic function disorder with a marked increase in AST (GOT), ALT (GPT), and γ-GTP levels etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

Company report

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	Osteoporosis (hyperlipidaemia, chronic gastritis)	60 mg 92 days	**Hepatic function disorder** 3 years before administration: The patient was diagnosed with osteoporosis. The treatment was started. 14 days before administration: Hepatic function tests etc. showed no abnormalities. On day 1 of administration: Administration of this drug was started. On day 91 of administration: The patient had faeces hard, followed by anal haemorrhage. On day 92 of administration (day of discontinuation): The patient visited hospital for anal haemorrhage. Although there were no subjective symptoms, blood sample confirmed hepatic function disorder. AST (GOT) was 777 IU/L, ALT (GPT) was 1134 IU/L, γ-GTP was 140 IU/L, and Al-P was 604 IU/L. Administration of all the drugs was discontinued.	Company report

				1 day after discontinuation: The patient was referred to another hospital and was hospitalized. She was treated by drip infusion alone. 24 day after discontinuation: The patient was discharged from the hospital. Afterwards, treatment involved out-patient observation was conducted. **<Test results>** DLST was implemented only for this drug: negative Hepatitis A, hepatitis B, CMV, EBV, antinuclear antibody, antimitochondrial antibody: negative Hepatitis C, hepatitis E, HIV, herpes: not performed IgG antibodies: within normal range Liver biopsy: although there was slight infiltration of eosinophils, marked infiltration was not confirmed. A definite diagnosis for the cause of hepatic function disorder could not be made.	
	Concomitant medications: alfacalcidol, atorvastatin calcium hydrate, roxatidine acetate hydrochloride, mosapride citrate, rebamipide				

Clinical Laboratory Values

	14 days before admin.	On day 92 of admin. (day of discontinuation)	1 day after discontinuation	7 days after discontinuation	21 days after discontinuation	27 days after discontinuation	43 days after discontinuation
AST (GOT) (IU/L)	26	777	696	363	131	87	31
ALT (GPT) (IU/L)	26	1134	1095	600	279	189	35
γ-GTP (IU/L)	21	140	125	—	102	101	46
Al-P (IU/L)	350	604	494	371	381	370	325
LDH (IU/L)	—	—	459	—	—	275	216
Total bilirubin (mg/dL)	—	—	1.6	1.4	—	1.5	0.9

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

2 Quetiapine Fumarate

Brand Name (name of company)	Seroquel Fine Granules 50%, Seroquel 25 mg and 100 mg Tablets (Shizuoka Fujisawa Co., Ltd.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

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

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, leucopenia: Agranulocytosis, leukopenia may occur. Patients should becarefully monitored through periodical blood testing etc. If any abnormalities are observed, appropriate measures such as drug discontinuation should be taken.

<Reference Information>

Company report

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 20s	Schizophrenia (parkinsonism, insomnia, pyrexia, constipation)	25 mg 5 days	**White blood cell decreased** Before administration of this drug, olanzapine (until 18 days before administration of this drug), haloperidol (until 13 days before administration of this drug), and risperidone (until 11 days before administration of this drug) were administered. In addition, biperiden hydrochloride, chlorpromazine/promethazine, cefotiam hydrochloride, and levofloxacin were also administered before administration of this drug. On day 1 of administration: Administration of this drug was started. On day 2 of administration: Pyrexia of 39.1°C developed. On day 3 of administration: Administration of cefotiam hydrochloride was started for the treatment of pyrexia. On day 5 of administration (day of discontinuation): Blood sample showed leukocyte count of 1700/mm^3 (granulocytes 68%). Administration of this drug was discontinued. 1 day after discontinuation: Pyrexia was alleviated. Administration of cefotiam hydrochloride was discontinued. White blood cell count was 2000/mm^3 (granulocytes 51%). 10 days after discontinuation: White blood cell count improved to 4300/mm^3.	Company report
	Concomitant medications: risperidone, biperiden hydrochloride, chlorpromazine/promethazine, olanzapine, haloperidol, cefotiam hydrochloride, levofloxacin, flunitrazepam, etizolam, nitrazepam, clarithromycin, sennoside, diazepam				

Clinical Laboratory Values

	2 days before admin.	On day 5 of admin. (day of discontinuation)	3 days after discontinuation	10 days after discontinuation
Body temperature (°C)	38.1	39.1	37.0	36.8
RBC (×10^4/mm^3)	420	457	405	414
Haemoglobin (g/dL)	13.4	14.5	12.8	13.2
Haematocrit (%)	40.0	43.2	38.3	40.7
WBC (/mm^3)	6400	1700	3200	4300
Neutrophils (%)	74.0	67.0	39.3	—
Neutrophils (stab cells) (%)	—	4.0	—	—
Neutrophils (segmented cells) (%)	—	63.0	—	—
Eosinophils (%)	5.8	1.0	10.4	—
Basophils (%)	0.9	0.0	1.3	—
Lymphocytes (%)	15.3	29.0	41.8	—
Monocytes (%)	4.0	3.0	7.2	—
PLT (×10^4/mm^3)	29.6	21.5	26.7	32.6

RBC: Red Blood Cell PLT: Platelet
WBC: WBC: White Blood Cell

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Male 50s	Schizophrenia (acute bronchitis, sleep loss, Parkinson's syndrome, chronic gastritis, chronic bronchitis)	100 mg 9 days	**Agranulocytosis** 3 days before administration: Administration of imipenem/cilastatin sodium was started for the treatment of acute bronchitis. CRP was 6.05 mg/dL, white blood cell count was 5800/mm^3. On day 1 of administration: Administration of this drug was started. On day 2 of administration: As CRP decreased to 0.44 mg/dL, administration of imipenem/cilastatin sodium was discontinued. On day 7 of administration: Pyrexia was not observed. General condition was good. On day 8 of administration: In the afternoon, pyrexia of 38.2ºC developed. Cooling was started. Administration of levomepromazine maleate, quazepam, and triazolam was discontinued. On day 9 of administration (day of discontinuation): In the morning, body temperature was 36.2ºC. Pulse rate was 72 beats/minute. In the afternoon, body temperature was 40.1ºC. Pulse rate was 112 beats/minute. Cooling was conducted again. Peripheral blood test showed status of agranulocytosis with white blood cell count of 600/mm^3 (neutrophils 18%). (CRP 9.22 mg/dL) Administration of all the drugs was discontinued. Sulbactam sodium/cefoperazone sodium was administered through drip infusion. The patient was transferred to another hospital for whole body control. 10 day after discontinuation: The patient was recovered from granulocytopenia (received call from the hospital to where patient was transferred). 11 day after discontinuation: The patient was hospitalized in this hospital again (for treatment of schizophrenia).	Company report
	Concomitant medications: imipenem/cilastatin sodium, bromperidol, chlorpromazine hydrochloride, quazepam, triazolam, levomepromazine maleate, mazaticol hydrochloride, rebamipide, ambroxol hydrochloride				

Clinical Laboratory Values

	3 days before admin.	On day 2 of admin.	On day 9 of admin. (day of discontinuation)
Body temperature (ºC)	37.2	37.4	40.1
RBC ($\times 10^4/mm^3$)	366	370	389
Haemoglobin (g/dL)	11.1	11.2	12.1
Haematocrit (%)	33.6	34.6	35.5
WBC ($/mm^3$)	5800	4300	600
Neutrophils (%)	55.0	24.6	18.0
Eosinophils (%)	5.6	6.5	—

Basophils (%)	0.4	0.8	—
Lymphocytes (%)	33.1	57.8	59.0
Monocytes (%)	4.6	3.3	22.0
PLT ($\times 10^4/mm^3$)	33.8	36.0	29.1
CRP (mg/dL)	6.05	0.44	9.22

RBC: Red Blood Cell
WBC: White Blood Cell
PLT: Platelet
CRP: C-Reactive Protein

3 Blood Glucose Self-monitoring Kit

(those using the glucose dehydrogenase method and coenzyme pyroloquinoline quinone)

Brand Name (name of company)	FreeStyle Kissei Sensor, Nipro FreeStyle Sensor (Nipro Corporation) Accu-Chek Compact Drum II, Accu-Chek Active Sticks, Accu-Chek Advantage Test Strips S (Roche Diagnostics K.K.) Glutest Neo Sensor, G Sensor (Matsushita-Kotobuki Electronics Industries, Ltd.)

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

[Warning]

WARNING

The following patients should not be treated with this product, since overestimation of blood glucose levels may occur.

Patients receiving infusion therapy solutions etc. (note: overestimation of blood glucose levels occurs when a patient is receiving infusions containing maltose.)

Patients receiving dialysis fluid containing icodextrin

Patients undergoing galactose tolerance test

Patients undergoing a xylose absorption test

Since it has been reported that symptoms of hypoglycaemia occurred in patients receiving infusion therapy solution at medical institutions as a result of administration of insulin based on blood glucose measurements taken using this kits, as a general rule, this device is intended for home use by patients for glucose monitoring.

<Reference Information> Company report

Case Summary

No.	Patient		Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 70s	Diabetes mellitus (cervical quadriplegia, cardiac failure congestive, chronic nephritis, ileus)	16 days	**Hypoglycaemia** On day 16 of use (day of discontinuation): The patient was not permitted to eat due to ileus, and 500 ml of maintenance fluid containing maltose was being administered 3 times/day via drip infusion. As the ileus was improving at the time of this event, food and drip infusion were concomitantly given. Blood glucose levels were 300–400 mg/dL when a self-monitoring glucose test that uses coenzyme GDH-PQQ was conducted. Although insulin human (Genetical recombination) was administered in 20–30 units on a sliding scale method, blood glucose levels did not improve and the amount of insulin was gradually increased.	Company report

				At night, the patient experienced seizure with loss of consciousness. Although the doctor on duty had difficulty in diagnosis due to blood glucose level of 299 mg/dL measured with the GDH-PQQ coenzyme self-monitoring glucose test at first, when measured in the examination room, blood glucose level was 26 mg/dL and hypoglycaemic attack was determined. Administration of 50% glucose injection at 40 mL was conducted as a treatment. 1 day after discontinuation: The patient recovered.	
	Concomitant medications: furosemide, sennoside, maintenance fluid containing maltose, insulin human (Genetical recombination)				

2

Revision of PRECAUTIONS

(No. 164)

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. 210) (excluding those presented in "1. Important Safety Information" of this Bulletin.), together with reference materials.

1 <Antihypertensives> Trandolapril

[Brand Name]	Odric Tablet 0.5 mg and 1 mg (Aventis Pharma Limited), Preran 0.5 mg and 1 mg Tablets (Chugai Pharmaceutical Co., Ltd.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Pancreatitis:** Pancreatitis may occur. If abnormalities are observed, appropriate measures, such as discontinuation of administration should be taken.
<Reference Information>	Company report

2 <Alkylating agents> Nimustine Hydrochloride

[Brand Name]	Nidran for Injection 25 mg and 50 mg (Sankyo Co., Ltd.)
[Warning]	**WARNING** Cancer chemotherapies including this drug should be conducted in medical institution that can provide emergency medical care under supervision of a physician with sufficient knowledge and experience in the chemotherapy, and only be indicated if it is appropriate to conduct this therapy. Caution should be exercised by referring to the package inserts for each concomitant medication in choosing patients indicated for this therapy. Patients or their family members should be fully advised of the efficacy and risks of this drug, and informed consent should be obtained from them before starting treatment.
[Precautions of Dosage and Administration]	Regarding concomitant therapies with other anticancer drugs in the treatment of astrocytoma malignant and gliomas containing constituent of oligodendrogliomas (procarbazine hydrochloride, nimustine hydrochloride, and vincristine sulfate), thoroughly read package inserts and related materials ["Anticancer drug report: procarbazine hydrochloride (brain tumour)", "Anticancer drug report: vincristine sulfate (brain cancer)" etc.] of concomitant drugs.
<Reference Information>	Company report

3 <Antimetabolites>
Tegafur/Gimeracil/Oteracil Potassium

[Brand Name] TS-1 Capsule 20 and 25 (Taiho Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Disseminated intravascular coagulation (DIC): Disseminated intravascular coagulation (DIC) may occur. Patients should be carefully monitored and if abnormalities are observed in blood tests relating to platelet count, serum FDP, and plasma fibrinogen concentration etc., administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

4 <Antineoplastics-Miscellaneous>
Penicillin-treated Lyophilized Powder of the Su-strain of Streptococcus Pyogenes (A group, type 3)

[Brand Name] Picibanil 0.2 KE, 0.5 KE, 1 KE, and 5 KE (Chugai Pharmaceutical Co., Ltd.)

[Important Precautions]

Since there is no certain method of predicting the onset of shock or anaphylactoid symptoms caused by this drug, following measures should be taken:

1) Ask appropriate questions regarding the patient's medical histories etc. beforehand. In addition, as this drug contains benzylpenicillin, the patient's allergic histories with antibiotics etc. should be confirmed.
2) Emergency measures against shock etc. must be prepared prior to administration.
3) Patients should be kept rested throughout administration and carefully monitored. In particular, patients should be carefully monitored immediately after the start of administration.
4) When recommencing administration after a period of cessation, the drug should be administered with careful attention beginning with small doses.

[Adverse Reactions (clinically significant adverse reactions)]

Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

5 <Biological preparations-Miscellaneous>
Anti-human T-lymphocyte Lmmunoglobulin, Rabbit

[Brand Name] Zetbulin Inj. (Nippon Zoki Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Platelet decreased: Since platelets decreased and aggravation of bleeding tendency may occur due to the administration of this drug, periodic measurement of platelet count should be conducted. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

[Clinically Significant Adverse Reactions (similar drugs)]

Interstitial pneumonia, pulmonary oedema: Interstitial pneumonia and pulmonary oedema may occur due to the administration of anti-human thymocyte immunoglobulin, equine. Patients should be carefully monitored. If abnormalities such as pyrexia, cough, dyspnoea, or chest X-ray abnormal are observed, administration should be discontinued and appropriate measures should be taken.

Bleeding tendency: Since bleeding tendency such as purpura, haematuria, epistaxis, bleeding spot subcutaneous, pulmonary haemorrhage, and haemorrhage of digestive tract may occur due to the administration of anti-human thymocyte immunoglobulin, equine, periodic blood testing should be conducted. If bleeding tendency is observed, administration should be discontinued and take appropriate measures should be taken.

	Serious liver disorder: Serious liver disorder may occur due to the administration of anti-human thymocyte immunoglobulin, equine, periodic blood testing should be conducted. If jaundice or significant transaminases increased etc. is observed, administration should be discontinued and take appropriate measures should be taken.
<Reference Information>	Company report