

Pharmaceuticals and Medical Devices Safety Information

No. 265 January 2010

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. 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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*This translation of the original Japanese text is for information purpose only
(in the event of inconsistency, the Japanese text shall prevail).*

Pharmaceuticals and Medical Devices Safety Information No. 265 January 2010

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	Handling of fire during Long-term Oxygen Therapy		Oxygen is a combustion enhancing gas. Package inserts and user manuals for oxygen concentrators, liquid oxygen units and oxygen cylinders (to be referred to as “oxygen concentrators, etc.” in the following) used for Long-term Oxygen Therapy (LTOT) contain an alert to the effect that fire should not be used near oxygen-providing equipment. Nevertheless, accidents involving deaths from fires likely caused by smoking, etc. in patients using oxygen concentrators, etc. have occurred repeatedly. Therefore, medical institutions have been instructed via the heads of prefectural public health bureaus to continuously alert patients and their families or caregivers to the danger of fire when using LTOT ¹⁾ . Precautions to be taken when applying LTOT are explained hereafter.	4
2	Sorafenib tosilate (and 4 others)	<i>P</i> <i>C</i>	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 November 18 and December 1, 2009.	7
3	Acemetacin (and 14 others)		Revision of PRECAUTIONS (No. 212)	21
4	Products subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of January 1, 2010.	26

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

To Pharmaceuticals and Medical Devices Safety Management Supervisor
—Please use our e-mail alert service—

The Pharmaceuticals and Medical Devices Agency is providing a “Pharmaceuticals and Medical Devices Information E-mail Alert Service” (<http://www.info.pmda.go.jp/info/idx-push.html>, Japanese only), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of PRECAUTIONS is issued. You are encouraged to register for and use the service.

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

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing 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.

Handling of fire during Long-term Oxygen Therapy

1. Introduction

Oxygen is a combustion enhancing gas (gas that helps things burn). Package inserts and user manuals for oxygen concentrators, liquid oxygen units and oxygen cylinders (to be referred to as “oxygen concentrators, etc.” in the following) used for Long-term Oxygen Therapy (LTOT) contain WARNINGS stating, for example, “Do not use the equipment close to fire (burn injury and fire may occur)” to alert users to the risk of fire.

Nevertheless, accidents involving death from fire believed to be caused by smoking, etc. in patients using oxygen concentrators, etc. have occurred repeatedly. Therefore, on January 15, 2010, medical institutions have been instructed via the heads of prefectural public health bureaus (departments) to continuously alert patients and their families or caregivers regarding the handling of fire during LTOT¹⁾. Precautions to be taken when using LTOT are explained hereafter.

2. Measures taken so far

The Japan Industrial and Medical Gases Association, a trade association of firms involved in the medical oxygen business (“Medical Gases Association”, in the following), made and distributed pamphlets and DVDs²⁾ about the issue. In June 2008, Pharmaceuticals and Medical Devices Agency (PMDA) released the PMDA Medical Safety Information No.4 entitled “Precautions against smoking and use of fire in Long-term Oxygen Therapy (LTOT)”, and several other measures have been taken to draw attention to the proper handling of fire during LTOT.

3. Cases of serious health damage

According to the survey by the Medical Gases Association, 27 cases of serious health damage due to fire in the homes of patients receiving LTOT from October 2003 to December 2009 were reported. The following table presents the details of these cases.

Cases of serious health damage due to fire in the homes of patients receiving LTOT

No.	Date of occurrence	Location (Prefecture)	Age (sex)	Health damage	Cause (including suspected cause)
1	December 2003	Shizuoka	70s (M)	Death (by fire)	Smoking
2	May 2004	Tokyo	80s (F)	Death	(Unknown; fire origin: kitchen)
3	February 2005	Tochigi	70s(M)	Death	Smoking
4	March 2005	Hiroshima	60s (M)	Death (by fire)	Smoking (in bed)
5	March 2005	Fukushima	80s (M)	Death (by fire)	Current leakage (electric blanket)
6	July 2005	Hyogo	60s (M)	Death (by fire)	Smoking
7	November 2005	Hiroshima	70s (M)	Death (by fire)	(Unknown; smoking in bed)
8	March 2006	Okayama	80s (M)	Death (by fire)	(Unknown)
9	May 2006	Tokyo	80s (M)	Death (burn injury)	Cigarette not put out properly
10	August 2006	Kyoto	80s (F)	Death (CO intoxication)	Smoking (in bed)
11	August 2006	Hyogo	60s (F)	Serious injury (burn injury) → Death	Smoking
12	October 2006	Kyoto	70s (M)	Death (by fire)	Smoking
13	December 2006	Kyoto	10s (F)	Death	Space heater
14	March 2007	Nagano	50s (M)	Death (by fire)	Smoking
15	March 2007	Aichi	40s (M)	Death (by fire)	(Unknown)
16	April 2007	Chiba	60s (M)	Death (by fire)	(Unknown)
17	May 2007	Hyogo	80s (F)	Serious injury (burn injury of the face)	Smoking
18	November 2007	Fukushima	80s (M)	Death	Smoking
19	December 2007	Tokyo	80s (F)	Death	(Unknown; fire origin: kitchen)
20	March 2008	Yamaguchi	70s (F)	Death	Smoking
21	November 2008	Tokyo	70s (M)	Death	Ignition of incense with a lighter
22	January 2009	Nara	≥90 (M)	Death (by fire)	Space heater
23	February 2009	Kagoshima	50s (M)	Death (by fire)	Smoking
24	March 2009	Chiba	80s (M)	Death (by fire)	Space heater or family altar
25	May 2009	Saitama	70s (F)	Death (by fire)	(Unknown; fire origin: near the power source)
26	October 2009	Kyoto	80s (M)	Death (by fire)	Smoking
27	November 2009	Hyogo	60s (F)	Death (by fire)	(Unknown)

Summarized by Medical Gases Division, Japan Industrial and Medical Gases Association (As of December 2009)

4. Request to healthcare providers

Medical providers are requested to give the following information and instructions to patients receiving LTOT and their families or caregivers.

- 1) Smoking and use of any other kind of fire during therapy with high-concentration oxygen may cause items such as cannulas and clothing to catch fire, resulting in severe burn injury and home fires.
- 2) Fire should not be used within 2 meters of an oxygen concentrators. Smoking is strictly prohibited while using oxygen.
- 3) Oxygen only does not cause items such as cannulas and clothing to catch fire and cause home fires when properly used in accordance with the user manual and with appropriate precautions against fire. Oxygen therapy should be used in accordance with the instructions given by the doctor, but should not lead to undue anxiety.

The Medical Gases Association provides materials for doctors to help them give the above information to their patients and their families regarding LTOT. Oxygen providers are also involved in calling attention to the fire precautions when visiting patients' homes⁴⁾.

5. Closing comments

For details of the alert, please refer to Ministry of Health, Labour, and Welfare (MHLW) website (<http://www.mhlw.go.jp/stf/houdou/2r98520000003m15.html>). (Japanese only)

Reference materials, such as relevant notifications, an educational leaflet, "Please be careful of handling fire and refrain from smoking during Long term Oxygen Therapy", prepared by MHLW, are also available for the use of readers^{5,6)}.

<References>

- 1) Joint Notification No. 0015-1 (dated January 15, 2010) of the General Affairs Division and Guidance of Medical Service Division, Health Policy Bureau, and Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare entitled "Handling of fire during Long-term Oxygen Therapy (Request for alert and provision of information to users)"
- 2) Japan Industrial and Medical Gases Association website
<http://www.jimga.or.jp/medical/special/dvd01.html>
- 3) Medical Safety Information No.4 of the Pharmaceuticals and Medical Devices Agency "Precautions against smoking and use of fire in Long-term Oxygen Therapy (LTOT)"
<http://www.pmda.go.jp/english/service/pdf/safety/No.4.pdf>
- 4) Notification No. 0015-3 (dated January 15, 2010) of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare "Handling of fire during Long-term Oxygen Therapy"
- 5) Educational pamphlet prepared by the Ministry of Health, Labour, and Welfare "Please be careful of handling fire and refrain from smoking during Long term Oxygen Therapy"
<http://www.mhlw.go.jp/stf/houdou/2r98520000003m15-img/2r98520000003m2n.pdf>
- 6) "Risk of fire during Long-term Oxygen Therapy", Kobe City Fire Bureau website
<http://www.city.kobe.lg.jp/safety/fire/information/zaitakusanso.html>

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 November 18 and December 1, 2009.

1 Sorafenib tosilate

Brand name (name of company)	Nexavar Tablets 200 mg (Bayer Yakuhin, Ltd.)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Radically non-resectable or metastatic renal cell carcinoma, unresectable hepatocellular carcinoma

《PRECAUTIONS (underlined parts are additions)》

[Important Precautions] Hepatic function disorder with elevations of AST (GOT) or ALT (GPT), jaundice, or hepatic failure may occur. Patients should be carefully monitored through periodic liver function tests during treatment.
Hepatic encephalopathy has been reported, mainly in patients with hepatocellular carcinoma or hepatic cirrhosis. When this drug is used in these patients, they should be monitored through blood ammonia test etc. and clinical symptoms, including disturbances in consciousness, should be carefully observed.

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder/jaundice, hepatic failure, hepatic encephalopathy:** Hepatic function disorder with elevations of AST (GOT) or ALT (GPT), jaundice, hepatic failure, or hepatic encephalopathy may occur. Patients should be carefully monitored, and if abnormalities are observed, the dose of the drug should be reduced or administration discontinued, and appropriate measures should be taken.
Hepatic encephalopathy has been reported, mainly in patients with hepatocellular carcinoma or hepatic cirrhosis. When this drug is used in these patients, they should be monitored through blood ammonia test etc. and clinical symptoms, including disturbances in consciousness, should be carefully observed.

<Reference Information> The number of reported adverse reactions (for which a causality to the drug could not be denied) over the last 1 year (April 2008 to October 31, 2009):

- Hepatic failure, hepatic encephalopathy: 21 cases (including 7 fatalities)

The number of patients treated with Sorafenib tosilate for a year estimated by marketing authorisation holder (MAH): approximately 3,700 (November 2008 to October 2009).
Marketed in Japan in: April 2008
Addition of indication of unresectable hepatocellular carcinoma: May 2009

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Hepatocellular carcinoma (lung metastasis, hepatitis C)	800 mg for 9 days	<p>Hepatic encephalopathy</p> <p>179 days before administration: Administration of 7.5 mg of zopiclone was started.</p> <p>15 days before administration: Contrast enhanced CT, cisplatin 100 mg + iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil, followed by intra-arterial injection of fluorouracil at 1250 mg/48 hours (second time). Child-Pugh score before administration: A, ECOG-PS: 0-1. The patient had never experienced an episode of encephalopathy before. Evaluation of hepatic tumors before administration: Number of tumors with diameter of 1 cm or greater; one mass of multiple tumors. Longest diameter: 16 cm.</p> <p>Day 1 of administration: Administration of this drug was started at 800 mg. From that time, the patient defecated 2 to 4 times a day until Day 9 of administration.</p> <p>Day 5 of administration: The patient fell on her buttocks on the bedside during the night.</p> <p>Day 6 of administration: The patient had no memory of the fall. She fell on the floor and sustained a cut of 1 cm in length around the left eyelid. A CT scan of the head revealed no abnormal findings.</p> <p>Day 7 of administration: Administration of zopiclone was discontinued. The patient complained of insomnia (until the next day).</p> <p>Day 9 of administration (day of discontinuation): She was able to talk after dinner. However, after that, she was unable to get out of bed. Administration of this drug was discontinued.</p> <p>1 day after discontinuation: Early in the morning, she did not wake up during diaper changing and was found to be in a somnolent state. Her vital signs were normal. Japan Coma Scale (JCS): III-200. In the same morning, the physician in charge examined the patient and found her to have JCS of III-200-300. CT scan of the head was normal. An increased level of ammonia was found. CT scan of the abdomen showed no change. A very small amount of ascites was found. Severe halitosis (ammonia odor) was present. The patient was diagnosed with hepatic encephalopathy and was given 500 mL of saline transfusion and intravenous infusion of 500 mL of amino acid in preparation for hepatic failure, but she did not awaken. Hepatic encephalopathy coma scale 4: coma. Reaction to pain and stimulus was present. The patient remained in a coma. Onset of hepatic coma.</p> <p>3 days after discontinuation: In the early hours, the patient died of hepatic encephalopathy and hepatic coma.</p>
Concomitant medications: Zopiclone, magnesium oxide, isoleucine/leucine/valine, betamethasone				

Clinical Laboratory Values

	72 days before administration	44 days before administration	16 days before administration	Day 6 of administration	Day 8 of administration	1 day after discontinuation
AST (GOT) (IU/L)	—	120	97	174	374	447
ALT (GPT) (IU/L)	—	29	18	33	47	54
LDH (IU/L)	—	392	391	529	991	1382
AI-P (IU/L)	—	1250	1083	1113	1125	1244
γ-GTP (IU/L)	—	254	206	140	136	153
Total bilirubin (mg/dL)	1.0	1.0	1.4	2.8	2.7	3.8
Albumin (g/dL)	3.6	3.9	4.1	4.0	3.7	3.8
PT-INR	1.22	1.13	1.17	—	1.37	1.56
Ammonia level (µg/dL)	—	—	—	—	150	259

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)

ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)

LDH: Lactate dehydrogenase

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Hepatocellular carcinoma (lung metastasis)	800 mg for 7 days	<p>Hepatic encephalopathy Date unknown: The patient received 250 mg of fluorouracil + 10 mg of cisplatin 5 days a week. Oral combination treatment with tegafur and uracil was also administered. Child-Pugh score before administration: A, ECOG-PS: 0.</p> <p>Day 1 of administration: Administration of this drug was started at 800 mg.</p> <p>Day 6 of administration: The patient developed hypertension.</p> <p>Day 7 of administration (day of discontinuation) The patient developed hand and foot syndrome (grade 2) and hepatic encephalopathy (coma grade 2). The patient was in a slightly somnolent state, stated he “felt dizzy” and showed mild flapping tremor. The ammonia level was increased to 144 µg/dL. The patient had never had hyperammonaemia before. Intravenous infusion of amino acid preparation for hepatic failure and oral lactitol hydrate was started on this day. This drug was discontinued. Subjective symptoms improved following the infusion of 500 mL of the amino acid preparation for hepatic failure. ECOG-PS: 0.</p> <p>4 days after discontinuation: The patient had been applying a moisturizing cream since the start of this drug administration, but not as much on the soles of his feet; the soles suddenly started aching on this day. The patient, who was not hypertensive in nature, developed hypertension with a blood pressure increasing to 180 mmHg, and was given 20 mg of nifedipine.</p> <p>5 days after discontinuation: The ammonia level became normal at 58 µg/dL. No symptoms of encephalopathy were observed. The amino acid infusion was switched to an oral amino acid preparation for hepatic failure.</p> <p>13 days after discontinuation: Hand and foot syndrome diminished. Hypertension and hepatic encephalopathy resolved. Since the ammonia level was stable at</p>

				the normal level of 33 µg/dL, treatment for hepatic encephalopathy was terminated.
Concomitant medications: Menatetrenone, Quercus salicina extract, ursodeoxycholic acid, magnesium oxide, lormetazepam, Juzen-taiho-to				

Clinical Laboratory Values

	5 days before administration	Day 5 of administration	Day 7 of administration (day of discontinuation)	2 days after discontinuation	5 days after discontinuation	10 days after discontinuation	13 days after discontinuation
AST (GOT) (IU/L)	30	47	63	56	58	37	33
ALT (GPT) (IU/L)	14	21	27	21	25	19	16
LDH (IU/L)	198	310	388	356	376	268	241
AI-P (IU/L)	272	334	348	288	310	285	290
γ-GTP (IU/L)	19	24	24	21	24	21	21
Total bilirubin (mg/dL)	0.81	2.08	2.70	2.76	2.26	0.98	1.01
Albumin (g/dL)	3.1	4.0	3.8	3.1	3.2	3.1	3.2
PT-INR	1.15	1.11	1.14	1.10	1.16	1.22	1.13
Ammonia (µg/dL)	—	—	144	157	58	72	33

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)

ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)

LDH: Lactate dehydrogenase

2 Aripiprazole, spiperone, sulpiride, zotepine, nemonapride, pipamperone hydrochloride, pimozide, moperone hydrochloride

Brand name (name of company)	<p>Aripiprazole Abilify Powder 1%, Abilify Tablets 3 mg, 6 mg, 12 mg, Abilify Oral Solution 0.1% (Otsuka Pharmaceutical Co., Ltd.)</p> <p>Spiperone Spiropitan Powder 0.3%, Spiropitan Tablets 0.25 mg and 1 mg (Sannova Co. Ltd.)</p> <p>Sulpiride Abilit Fine Granules 10%, 50%, Abilit Tablets 50 mg, 100 mg, 200 mg, Abilit Capsules 50 mg (Dainippon Sumitomo Pharma Co., Ltd.) Dogmatyl Fine Granules 10%, 50%, Dogmatyl Tablets 50 mg, 100 mg, 200 mg, Dogmatyl Capsules 50 mg, Dogmatyl Intramuscular Injection 50 mg, 100 mg (Astellas Pharma Inc.) Coolspan Tablets 50 (Nipro Pharma Corporation) Keityl (Sankei Yakuhin K.K.) Skanozen Tablets 100 (Tsuruhara Pharmaceutical Co., Ltd.) Sulpiride Tablets 50 mg “CH” (Choseido Pharmaceutical Co., Ltd.) Sulpiride Tablets 50 mg “TYK”, 100 mg “TYK”, 200 mg “TYK”, Sulpiride Capsules (Taisho Pharmaceutical Industries, Ltd.) Sulpiride Fine Granules 10% “Amel”, 50% “Amel”, Sulpiride Tablets 50 mg “Amel”, 100 mg “Amel”, 200 mg “Amel” (Kyowa Pharmaceutical Industry Co., Ltd.) Sulpiride Tablets 50 mg “Taiyo” (Taiyo Yakuhin Co., Ltd.) Sulpiride Tablets 100 mg “Towa”, 200 mg “Towa”, Sulpiride Capsules 50 mg “Towa” (Towa Pharmaceutical Co., Ltd.) Pyrikappl Capsules 50 mg, Pyrikappl Intramuscular Injection 50 mg (Isei Co., Inc.) Betamac Tablets 50 mg, 100 mg, 200 mg (Sawai Pharmaceutical Co., Ltd.)</p>
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	<p>Margenol Tablets 50 mg, Margenol Capsules 50 mg (Tatsumi Kagaku Co., Ltd.) Miradol Fine Granules 10%, 50%, Miradol Tablets 50, 100, 200, Miradol Capsules 50 mg (Bayer Yakuhin, Ltd.) Youmathyle Capsules 50 mg (Yoshindo Inc.)</p> <p>Zotepin Lodopin Fine Granules 10%, 50%, Lodopin Tablets 25 mg, 50 mg, 100 mg (Astellas Pharma Inc.) Setous Fine Granules 10%, 50%, Setous Tablets 25 mg, 50 mg, 100 mg (Takata Seiyaku Co., Ltd.) Majorpin Fine Granules 10%, 50%, Majorpin Tablets 25 mg, 50 mg, 100 mg (Kyowa Pharmaceutical Industry Co., Ltd.) Losizopilon Fine Granules 10%, Losizopilon Tablets 25 mg, 50 mg (Choseido Pharmaceutical Co., Ltd.)</p> <p>Nemonapride Emilace Fine Granules 2%, Emilace Tablets 3 mg, 10 mg (Astellas Pharma Inc.)</p> <p>Pipamperone Hydrochloride Propitan Powder 10%, Propitan Tablets 50 mg (Sannova Co. Ltd.)</p> <p>Pimozide Orap Fine Granules 1%, Orap Tablets 1 mg, 3 mg (Astellas Pharma Inc.)</p> <p>Moperone hydrochloride Luvatren Powder, Luvatren Tablets (Astellas Pharma Inc.)</p>
Therapeutic Category	Psychotropics
Indications	<p>Schizophrenia Symptoms stated below accompanying autistic spectrum disorder and mental retardation in children (for pimozide only) Abnormal behavior regarding motion, emotion, motivation, and interpersonal relations, etc. Pathological symptoms regarding sleep, diet, excretion, and speech, etc. Psychiatric symptoms involving stereotypy, etc.</p>

《PRECAUTIONS (underlined parts are additions)》

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, white blood cell decreased: Agranulocytosis and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration of the drug should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 3 years (April 1, 2006 to July 10, 2009):

- Agranulocytosis, white blood cell decreased: 8 cases (including 1 fatality)
- The number of patients treated with Aripiprazole, Spiperone, Sulpiride, Zotepine, Nemonapride, Pipamperone hydrochloride, Pimozide, Moperone hydrochloride for a year estimated by MAH: approximately 702,000 (FY 2008)

Marketed in Japan in:

- March 1965: Pipamperone hydrochloride
- February 1969: Spiperone
- August 1971: Moperone hydrochloride
- August 1973: Sulpiride
- April 1974: Pimozide
- February 1982: Zotepine
- May 1991: Nemonapride
- June 2006: Aripiprazole

Case Summary

<Aripiprazole>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Schizophrenia (diabetes mellitus)	10 mg for 14 days ↓ 15 mg for 20 days	<p>Leukopenia, hepatic function abnormal</p> <p>35 days before administration: Administration of gliclazide was started.</p> <p>28 days before administration: WBC: 3210/mm³</p> <p>Day 1 of administration: Administration of 10 mg of this drug was started in addition to the pretreatment drugs.</p> <p>Day 15 of administration: The dose of risperidone was reduced from 10 mg to 8 mg, and the dose of this drug was increased to 15 mg.</p> <p>Day 33 of administration: Pyrexia (38.6°C) was observed, and levofloxacin hydrate was prescribed (only for this day).</p> <p>Day 34 of administration (day of discontinuation): WBC was 820/mm³. A diagnosis of pneumonia was made by chest X-ray. Hepatic function abnormal (AST (GOT) 288 IU/L, ALT (GPT) 253 IU/L) was observed. All medications were discontinued. Cefepime dihydrochloride hydrate and lenograstim (genetical recombination) were prescribed (only for this day). Oxygen (5 L) was administered (only for this day). Later, the patient was transferred to another hospital. The patient received a tracheostomy, but her family refused use of a respirator.</p> <p>4 days after discontinuation: The patient died. (The cause of death: severe pneumonia due to opportunistic infection associated with white blood cell decreased, autopsy: not performed)</p>
Concomitant medications: Gliclazide, biperiden hydrochloride, flunitrazepam, risperidone				

Clinical Laboratory Values

	57 days before administration	28 days before administration	Day 13 of administration	Day 33 of administration	Day 34 of administration (day of discontinuation)
Body temperature (°C)	—	—	—	38.6	—
RBC (×10 ⁴ /mm ³)	334	348	347	—	290
Hemoglobin (g/dL)	10.5	11.1	11.0	—	9.4
Hematocrit (%)	31.3	32.6	33.0	—	26.6
WBC (/mm ³)	4170	3210	4010	—	820
Neutrophils (%)	72.4	75.1	71.2	—	93.9
Eosinophils (%)	0.5	0.3	0.2	—	0
Basophils (%)	0.2	0.3	0.2	—	0
Lymphocytes (%)	21.1	19.8	22.7	—	3.7
Monocytes (%)	5.8	6.5	5.7	—	2.4
PLT (×10 ⁴ /mm ³)	20.9	19.6	21.7	—	13.6
Blood glucose (fasting) (mg/dL)	102	100	100	—	79
AST (GOT) (IU/L)	21	20	25	—	288
ALT (GPT) (IU/L)	17	20	23	—	253

γ -GTP (IU/L)	17	17	19	—	29
LDH (IU/L)	256	221	247	—	255
BUN (mg/dL)	16.8	17.8	20.2	—	23.2
Creatinine (mg/dL)	0.88	0.76	0.98	—	0.74
CRP (mg/dL)	—	0.18	0.08	—	25.77
MCV (fL)	—	93.7	95.1	—	91.7
MCH (pg)	—	31.9	31.7	—	32.4
MCHC (g/dL)	—	34	33.3	—	35.3
HbA _{1c} (%)	—	5.4	5.4	—	5.2

AST (GOT): Aspartate aminotransferase (Glutamate oxaloacetate transferase)

ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase)

LDH: Lactate dehydrogenase

3 Olanzapine, risperidone (oral dosage form), risperidone (injectable dosage form)

1 Olanzapine, risperidone (oral dosage form)

Brand name (name of company)	<p>Olanzapine Zyprexa Fine Granule 1%, Zyprexa Tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Zydis Tablets 5 mg, 10 mg (Eli Lilly Japan K.K.)</p> <p>Risperidone (oral dosage form) Risperdal Fine Granule 1%, Risperdal Tablets 1 mg, 2 mg, 3 mg, Risperdal Oral Solution 1 mg/mL, Risperdal OD Tablets 0.5 mg, 1 mg, 2 mg (Janssen Pharmaceutical K.K.) Risperidone Fine Granule 1% "CH", Risperidone Tablets 1 mg "CH", 2 mg "CH", (Choseido Pharmaceutical Co., Ltd.) Risperidone Fine Granule 1% "MEEK", Risperidone Tablets 1 "MEEK", 2 "MEEK", 3 "MEEK" (Kobayashi Kako Co., Ltd.) Risperidone Fine Granule 1% "NP", Risperidone Tablets 0.5 mg "NP", 1 mg "NP", 2 mg "NP", 3 mg "NP" (Nipro Pharma Corporation) Risperidone Fine Granule 1% "NT", Risperidone Tablets 0.5 mg "NT", 1 mg "NT", 2 mg "NT", 3 mg "NT" (Nipro Genepha Corporation) Risperidone Fine Granule 1% "Amel", Risperidone Tablets 1 mg "Amel", 2 mg "Amel", 3 mg "Amel", Risperidone Oral Solution 1 mg/mL "Amel", Risperidone Oral Solution Divided Pack 0.5 mg "Amel", 1 mg "Amel", 2 mg "Amel", 3 mg "Amel", Risperidone OD Tablets 1 mg "Amel", 2 mg "Amel" (Kyowa Pharmaceutical Industry Co., Ltd.) Risperidone Fine Granule 1% "Ohara", Risperidone Tablets 1 "Ohara", 2 "Ohara", 3 "Ohara" (OHARA Pharmaceutical Co., Ltd.) Risperidone Fine Granule 1% "Sawai", Risperidone Tablets 1 mg "Sawai", 2 mg "Sawai", 3 mg "Sawai", Risperidone Oral Solution 1 mg/mL (Sawai), Risperidone OD Tablets 1 mg "Sawai", 2 mg "Sawai" (Sawai Pharmaceutical Co., Ltd.) Risperidone Tablets 1 mg "Sandoz", 2 mg "Sandoz", 3 mg "Sandoz" (Sandoz K.K.) Risperidone Fine Granule 1% "Taiyo", Risperidone Tablets 1 mg "Taiyo", 2 mg "Taiyo", 3 mg "Taiyo" (Taiyo Yakuhin Co., Ltd.) Risperidone Fine Granule 1% "Takata", Risperidone Tablets 1 mg "Takata", 2 mg "Takata", 3 mg "Takata", Risperidone Oral Solution 1 mg/mL (Takata), Risperidone OD Tablets 1 mg "Takata", 2 mg "Takata", 3 mg "Takata" (Takata Seiyaku Co., Ltd.) Risperidone Fine Granule 1% "Towa", Risperidone Tablets 1 mg "Towa", 2 mg "Towa", 3 mg "Towa", Risperidone Oral Solution 1 mg/mL "Towa", Risperidone OD Tablets 1 mg "Towa", 2 mg "Towa", (Towa Pharmaceutical Co., Ltd.)</p>
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	Risperidone Fine Granule 1% “Mylan”, Risperidone Tablets 1 mg “Mylan”, 2 mg “Mylan”, 3 mg “Mylan”, Risperidone Oral Solution Divided Pack 0.5 mg “Mylan”, 1 mg “Mylan”, 2 mg “Mylan” (Mylan Seiyaku Ltd.) Risperidone Fine Granule 1% “Yoshitomi”, Risperidone Tablets 0.5 mg “Yoshitomi”, 1 mg “Yoshitomi”, 2 mg “Yoshitomi”, 3 mg “Yoshitomi” (Zensei Pharmaceutical Industries Co., Ltd.) Risperidone Oral Solution 1 mg/mL “Yoshitomi” (Dojin Iyaku Kako Co., Ltd.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

《**PRECAUTIONS** (underlined parts are additions)》

[Important Precautions] Hypoglycaemia may occur. During administration of this drug, caution should be exercised regarding the onset of symptoms of hypoglycaemia such as feeling of weakness, malaise, cold sweat, tremor, somnolence, and disturbances in consciousness and patients should be monitored carefully, e.g. by measuring blood glucose levels.
Prior to initiation of treatment with this drug, patients and their families should be given adequate information about the possibility of the occurrence of the above adverse reactions and to watch for symptoms of hyperglycaemia (thirst, excessive drinking, polyuria, and pollakiuria, etc.) and symptoms of hypoglycaemia (feeling of weakness, malaise, cold sweat, tremor, somnolence, disturbance in consciousness, etc.). Patients should be instructed to discontinue this drug and consult a doctor immediately if such symptoms develop.

[Adverse Reactions (clinically significant adverse reactions)] **Agranulocytosis, white blood cell decreased:** Agranulocytosis and white blood cell decreased may occur. Patients should be monitored carefully, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.
Hypoglycaemia: Hypoglycaemia may occur. If symptoms of hypoglycaemia such as feeling of weakness, malaise, cold sweat, tremor, somnolence, and disturbances in consciousness are observed, drug administration should be discontinued and appropriate measures should be taken.

② **Risperidone (injectable dosage form)**

Brand name (name of company)	Risperdal Consta Intramuscular Injections 25 mg, 37.5 mg, 50 mg (Janssen Pharmaceutical K.K.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

《**PRECAUTIONS** (underlined parts are additions)》

[Important Precautions] Hypoglycaemia may occur. During administration of this drug, caution should be exercised regarding the onset of symptoms of hypoglycaemia such as feeling of weakness, malaise, cold sweat, tremor, somnolence, and disturbances in consciousness and patients should be monitored carefully, e.g. by measuring blood glucose levels.
Prior to initiation of the treatment with this drug, patients and their families should be given adequate information about the possibility of the occurrence of the above adverse reactions and to watch for symptoms of hyperglycaemia (thirst, excessive drinking, polyuria, and pollakiuria, etc.) and symptoms of hypoglycaemia (feeling of weakness, malaise, cold sweat, tremor, somnolence, disturbances in consciousness, etc.). Patients should be instructed to discontinue this drug and consult a doctor immediately if such symptoms develop.

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, white blood cell decreased: Agranulocytosis and white blood cell decreased may occur. Patients should be monitored carefully, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Hypoglycaemia: Hypoglycaemia may occur. If symptoms of hypoglycaemia such as feeling of weakness, malaise, cold sweat, tremor, somnolence, and disturbances in consciousness are observed, drug administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 3 years:

(April 1, 2006 to July 10, 2009)

- Agranulocytosis, white blood cell decreased: 6 cases (no fatalities)

(April 1, 2006 to November 6, 2009)

- Hypoglycaemia: 2 cases (no fatalities)

The number of patients treated with Olanzapine, Risperidone for a year estimated by MAH: approximately 2,013,000 (October 2008 to September 2009)

Marketed in Japan in: June 1996 (Risperidone)

June 2001 (Olanzapine)

Case Summary

<Olanzapine>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 20s	Schizophrenia (none)	20 mg for 34 days	<p>Granulocyte count decreased</p> <p>History of prior treatment: The patient had received this drug in another hospital (internal medicine) and developed hepatic symptoms. The symptoms were considered to be drug-induced liver disorder due to this drug, and the drug was discontinued.</p> <p>Day 1 of administration: After the patient had been transferred and admitted to our hospital, treatment with this drug at 20 mg, sodium valproate at 400 mg, and haloperidol at 2 mg were started for stabilization of psychiatric symptoms.</p> <p>Day 2 of administration: Laboratory test values: The white blood cell count was 7800/mm³, with 0% basophils, 2% eosinophils, 58% neutrophils, 34% lymphocytes, and 6% monocytes, the platelet count was 33.4 x 10⁴/mm³. The liver function test values were elevated (AST (GOT) 40 IU/L, ALT (GPT) 74 IU/L, LDH 212 IU/L, ALP 196 IU/L, and γ-GTP 67 IU/L).</p> <p>Day 9 of administration: AST (GOT) was 56 IU/L, ALT (GPT) 111 IU/L, LDH 203 IU/L, and γ-GTP 60 IU/L</p> <p>Day 21 of administration: Tiopronin at 300 mg was administered, and the liver function test values returned to normal (AST (GOT) 33 IU/L, ALT (GPT) 68 IU/L, LDH 184 IU/L, and γ-GTP 50 IU/L).</p> <p>About 3 weeks of administration: A decrease in granulocytes was observed with increasing body temperature. The body temperature remained high at close to 40°C for one week. The test for antinuclear antibodies was negative.</p> <p>Day 28 of administration: Laboratory test values: The body temperature was 40°C, the</p>

				<p>white blood cell count was 3700/mm³ with 1% basophils, 2% eosinophils, 22% neutrophils, 57% lymphocytes, and 12% monocytes; the platelet count was 17.9 x 10⁴/mm³.</p> <p>Day 34 of administration (day of discontinuation): Laboratory test values: The body temperature was 39°C, the white blood cell count was 2100/mm³ with 0% basophils, 6% eosinophils, 18% neutrophils, 57% lymphocytes, and 19% monocytes, the platelet count was 15.8 x 10⁴/mm³. This drug and sodium valproate were discontinued and switched to quetiapine fumarate. Later, the granulocyte count returned to normal.</p> <p>14 days after discontinuation: Laboratory test values: The body temperature was 36.6°C, the white blood cell count was 4300/mm³ with 1% basophils, 2% eosinophils, 49% neutrophils, 42% lymphocytes, and 6% monocytes; the platelet count was 30.5 x 10⁴/mm³.</p>
Concomitant medications: Sodium valproate, haloperidol				

Clinical Laboratory Values

	Day 2 of administration	Day 28 of administration	Day 34 of administration (day of discontinuation)	14 days after discontinuation
WBC (/mm ³)	7800	3700	2100	4300
Basophils (%)	0	1	0	1
Eosinophils (%)	2	2	6	2
Neutrophils (%)	58	22	18	49
Lymphocytes (%)	34	57	57	42
Monocytes (%)	6	12	19	6
PLT (x10 ⁴ /mm ³)	33.4	17.9	15.8	30.5
Hemoglobin (g/dL)	14.0	15.3	12.8	13.5
Body temperature (°C)	36.6	40	39	36.6

<Olanzapine>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Schizophrenia (none)	10 mg for 7 days	<p>Hypoglycaemic unconsciousness</p> <p>Medical history: The patient had no history of loss of consciousness or stroke, or any history related to hypoglycaemia such as gastrectomy or hepatic function disorder. Encephalogram was normal.</p> <p>History of prior treatment: The patient was admitted for chronic, treatment-resistant schizophrenia and treated with haloperidol, levomepromazine maleate, flunitrazepam, and biperiden hydrochloride. No adverse reaction was observed during treatment. The body mass index (BMI) was 19.8. Before administration of this drug, the fasting blood glucose level was 86 mg/dL and fasting insulin value was 5 µU/mL.</p> <p>Day 1 of administration: This drug at 10 mg was added after a blood test confirmed that the patient had no metabolic abnormality.</p> <p>Day 4 of administration: In the morning, the patient suddenly lost consciousness when walking. He did not appear to have suffered a stroke. A blood test performed in the unconscious state revealed hypoglycaemia</p>

				<p>(fasting glucose: 44 mg/dL) and increased insulin value (fasting insulin: 23 µU/mL). The HOMA insulin resistance index was 2.5. The triglyceride level was normal (88 mg/dL). The patient's consciousness rapidly recovered after i.v. injection of 20 mL of 50% glucose.</p> <p>Day 5 of administration: Early in the morning, the patient was discovered in a state of hypoglycaemic unconsciousness. Consciousness returned after i.v. injection of glucose.</p> <p>Day 6 of administration: Early in the morning, the patient was discovered in a state of hypoglycaemic unconsciousness. Consciousness returned after i.v. injection of glucose.</p> <p>Day 7 of administration (day of discontinuation): This drug was discontinued. The fasting glucose level was 87 mg/dL, and insulin value was 6 µU/mL. Then, the treatment was continued with typical antipsychotic drugs for 1 year, and then switched to risperidone at 2 mg.</p> <p>About 1 year after discontinuation: For the next two years following the switch, partial remission of chronic schizophrenia was achieved with risperidone at 3 mg.</p> <p>About 3 years after discontinuation: For 3 years after discontinuation of this drug, the patient experienced no hypoglycaemic unconsciousness and his blood glucose level remained normal.</p>
Concomitant medications: haloperidol, levomepromazine maleate, flunitrazepam, biperiden hydrochloride				

Clinical Laboratory Values

	Before administration	Day 4 of administration	7 days after administration (day of discontinuation)
Fasting blood glucose level (mg/dL)	86	44	87
Fasting insulin value (µU/mL)	5	23	6

4 Quetiapine fumarate

Brand name (name of company)	Seroquel Fine Granule 50%, Seroquel 25 mg Tablets, 100 mg Tablets, 200 mg Tablets (Astellas Pharma Inc.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

«PRECAUTIONS (underlined parts are additions)»

[Important Precautions]	<p><u>Hypoglycaemia may occur. During administration of this drug, caution should be exercised regarding the onset of symptoms of hypoglycaemia such as feeling of weakness, malaise, cold sweat, tremor, somnolence, and disturbances in consciousness, and patients should be monitored carefully, e.g. by measuring blood glucose levels.</u></p> <p>Prior to initiation of the treatment with this drug, patients and their families should be given adequate information about the possibility of the occurrence of the above adverse reactions and to watch for <u>symptoms of hyperglycaemia</u> (thirst, excessive drinking, polyuria, and pollakiuria, etc.) <u>and symptoms of hypoglycaemia</u> (feeling of weakness, malaise, cold sweat, tremor, somnolence, disturbances in consciousness, etc.). Patients should be instructed to discontinue this drug and consult a doctor immediately if such symptoms develop.</p>
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**[Adverse Reactions
(clinically significant
adverse reactions)]**

Hypoglycaemia: Hypoglycaemia may occur. If symptoms of hypoglycaemia such as feeling of weakness, malaise, cold sweat, tremor, somnolence, and disturbances in consciousness are observed, the drug should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 3 years (April 1, 2006 to November 6, 2009):

- Hypoglycaemia: 2 cases (no fatalities)

The number of patients treated with Quetiapine fumarate for a year estimated by MAH: approximately 220,000 (FY 2008).
Marketed in Japan in: February 2001

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Delirium (Parkinsonism- dementia complex)	50 mg for approx. 4 years and 7 months	<p>Hypoglycaemia</p> <p>History of prior treatment: The patient was on treatment for Parkinsonism-dementia complex with levodopa benserazide hydrochloride for 6 years and amantadine hydrochloride for 2 years.</p> <p>8 months before administration: The blood glucose level was 86 mg/dL.</p> <p>Day 1 of administration: Administration of this drug was started at 50 mg for delirium.</p> <p>2 years and 9 months of administration: The patient became unable to tolerate oral intake and enteral nutrition was started.</p> <p>3 years and 4 months of administration: Zopiclone was started for the treatment of insomnia</p> <p>4 years and 2 months of administration: Sarpogrelate hydrochloride was started for the treatment of peripheral circulatory disturbance in the extremities.</p> <p>4 years and 7 months of administration (day of discontinuation): The patient presented with heavy breathing and somnolence. Examination revealed pneumonia and the patient was admitted to the hospital. Hematology revealed hypoglycaemia with a blood glucose level of 48 mg/dL. An i.v. injection of 40 mL of 50% glucose was administered. The blood glucose level rose to 144 mg/dL. The treatment for pneumonia was continued at the same time.</p> <p>Using a nasogastric tube, 25 mg of this drug, sarpogrelate hydrochloride, levodopa benserazide hydrochloride, and amantadine hydrochloride were administered. Later, this drug was discontinued.</p> <p>1 day after discontinuation: The blood glucose level was 80 mg/dL. Following i.v. injection of 40 mL of 50% glucose, the blood glucose level was 20 mg/dL. Continuous drip infusion of glucose was given in addition to 40 mL of 50% glucose. The blood glucose level recovered to 132 mg/dL and remission of hypoglycaemia was achieved.</p> <p>2 days after discontinuation: The blood glucose level was 158 mg/dL.</p> <p>6 days after discontinuation: The patient died. (The cause of death was pneumonia. The death was not related to this drug.)</p>

Concomitant medications: Levodopa benserazide hydrochloride, amantadine hydrochloride, sarpogrelate hydrochloride, zopiclone, enteral nutrient
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5 Tandospirone citrate

Brand name (name of company)	Sediel Tablets 5 mg, 10 mg, 20 mg (Dainippon Sumitomo Pharma Co., Ltd.) Tandospirone Citrate Tablets 5 mg “Amel”, 10 mg “Amel”, 20 mg “Amel” (Kyowa Pharmaceutical Industry Co., Ltd.) Tandospirone Citrate Tablets 5 mg “Sawai”, 10 mg “Sawai”, 20 mg “Sawai” (Sawai Pharmaceutical Co., Ltd.) Tandospirone Citrate Tablets 5 mg “Towa”, 10 mg “Towa”, 20 mg “Towa” (Towa Pharmaceutical Co., Ltd.) Tandospirone Citrate Tablets 5 mg “Nichi-Iko”, 10 mg “Nichi-Iko”, 20 mg “Nichi-Iko” (Nichi-Iko Pharmaceutical Co., Ltd.)
Therapeutic Category	Hypnotics and sedatives, anxiolytics
Indications	Somatic symptoms in psychosomatic disease (autonomic dystonia, essential hypertension, peptic ulcer), depression, anxiety, feeling irritated, and sleep disorder Depression and phobia in neurosis

《**PRECAUTIONS** (underlined parts are additions)》

**[Adverse Reactions
(clinically significant
adverse reactions)]**

Neuroleptic malignant syndrome: Neuroleptic malignant syndrome may occur when this drug is used concurrently with antipsychotic agents, antidepressants, etc. or in association with a rapid dose reduction or discontinuation of tandospirone citrate. If symptoms such as pyrexia, disturbances in consciousness, severe muscle rigidity, involuntary movement, sweating, and tachycardia develop, appropriate measures such as cooling the body and fluid replacement should be taken. Increases in white blood cell count and serum CK (CPK) are often observed in association with neuroleptic malignant syndrome, and renal function may decrease accompanied by myoglobinuria.

<Reference Information>

The number of reported adverse reactions (for which a causality to the drug could not be denied) in about the last 3 years (April 1, 2006 to October 14, 2009):

- Neuroleptic malignant syndrome: 1 case (no fatalities)

The number of patients treated with Tandospirone citrate for a year estimated by MAH: approximately 343,000 (FY 2008).

Marketed in Japan in: December 1996

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Neurosis (Radius fracture, angina pectoris, dementia, cerebral infarction, asthenia)	30 mg for 4 days	Neuroleptic malignant syndrome The patient presented with injuries from fall. She had laceration in the head and was treated by a brain surgeon. She was diagnosed with left distal radial epiphyseal fracture, which was immobilized with a cast. She was admitted to the orthopedic department for rest. 1 day before administration: The patient complained of chest pain and was referred to the internal medicine department. She showed restlessness during the examination and was administered i.v. drip infusion of haloperidol. Day 1 of administration:

				<p>Administration of this drug was started.</p> <p>Day 2 of administration: Since her restless state persisted, the patient was referred to the psychiatric department. The body temperature was in the high 37s°C. The CK (CPK) was slightly elevated and myoglobin was elevated. Extrapyramidal disorder (muscle rigidity, cogwheel phenomenon) due to haloperidol was diagnosed. (Onset of malignant syndrome) Biperiden lactate was administered by i.v. infusion to treat the extrapyramidal disorder. With additional fluid replacement, the symptoms improved temporarily.</p> <p>Day 5 of administration (day of discontinuation): This drug was discontinued.</p> <p>1 day after discontinuation: The body temperature was 38°C, the blood pressure was 180-200 mmHg, pulse rate was 110-140/min., and WBC, CK (CPK) and myoglobin were increased. A causal relationship between the increase in myoglobin and this drug could not be denied. Her symptoms met the criteria for a diagnosis of neuroleptic malignant syndrome. Dantrolene sodium hydrate at 40 mg was administered by i.v. injection (for 5 days).</p> <p>4 days after discontinuation: The body temperature was 36°C, and some improvement was observed in the neuroleptic malignant syndrome.</p> <p>6 days after discontinuation: The patient received 100 mg of oral dantrolene sodium hydrate (for 4 days).</p> <p>9 days after discontinuation: The patient recovered from neuroleptic malignant syndrome.</p>
Concomitant medications: Haloperidol, isosorbide mononitrate, isosorbide dinitrate, hydroxyzine hydrochloride, verapamil hydrochloride, biperiden lactate				

Clinical Laboratory Values

	Day 1 of administration	Day 2 of administration	Day 3 of administration	1 day after discontinuation	4 days after discontinuation	14 days after discontinuation
WBC (/mm ³)	—	—	—	12200	9300	12200
CRP (mg/dL)	0.27	—	—	10.53	10.28	2.40
BUN (mg/dL)	—	14	10	21	17	14
Serum creatinine (mg/dL)	—	0.7	0.7	0.6	0.6	0.6
CK (CPK) (IU/L)	65	248	211	373	146	24
Myoglobin (ng/mL)	—	—	76	124	—	—

Revision of PRECAUTIONS

(No. 212)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated December 1, 2009 (excluding those presented in “2. Important Safety Information” of this Bulletin).

1 <Antipyretics and analgesics, anti-inflammatory agents>

Acemetacin

[Brand Name] RANTUDIL KOWA TAB. 30 mg (Kowa Co, Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] <Adverse reactions to acemetacin>
Gastrointestinal perforation, haemorrhage of digestive tract, gastrointestinal ulcers, or colitis haemorrhagic may occur. If any such symptoms are observed, administration should be discontinued immediately and appropriate measures should be taken.
 <Adverse reactions to indometacin, the active metabolite of acemetacin>
Intestinal stenosis/obstruction, colitis ulcerative have been reported in association with indometacin. If any such symptoms are observed, administration should be discontinued and appropriate measures should be taken.

<Psychotropics>

Oxypertine
 Carpipramine hydrochloride hydrate
 Carpipramine maleate
 Clocapramine hydrochloride hydrate
 Sultopride hydrochloride
 Timiperone
 2 Trifluoperazine maleate
 Fluphenazine decanoate
 Fluphenazine maleate
 Bromperidol
 Perphenazine
 Perphenazine hydrochloride
 Perphenazine fendizoate
 Perphenazine maleate
 Mosapramine hydrochloride

[Brand Name] Forit Powder 10%, Forit Tablets 20 mg, 40 mg (Daiichi Sankyo Co. Ltd.)
 Defekton Sugar-coated Tablets 25 mg, 50 mg (Mitsubishi Tanabe Pharma Corp.)
 Defekton Powder 10% (Mitsubishi Tanabe Pharma Corp.)
 Clofekton Granule 10% (Mitsubishi Tanabe Pharma Corp.), Clofekton Tablets 10 mg, 25 mg, 50 mg (Zensei Pharmaceutical Industries Co., Ltd.), and others
 Barnetil Fine Granule 50%, Barnetil Tablets 50, 100, 200 (Bayer Yakuhin, Ltd.), and others
 Tolopelon Fine Granule 1%, Tolopelon Tablets 0.5 mg, 1 mg, 3 mg, Tolopelon Injection 4 mg (Daiichi Sankyo Co., Ltd.), and others

Trifluoperazine Powder 1% “Mitsubishi”, Trifluoperazine Sugar-coated Tablets “Yoshitomi” (2.5), (5), (Mitsubishi Tanabe Pharma Corp.)
 Fludecasin Intramuscular Injection 25 mg, Fludecasin Kit Intramuscular Injection 25 mg (Mitsubishi Tanabe Pharma Corp.)
 Flumezin Powder 0.2%, Flumezin Sugar-coated Tablets (0.25), (0.5), (1) (Mitsubishi Tanabe Pharma Corp.)
 Impromen Fine Granule 1%, Impromen Tablets 1 mg, 3 mg, 6 mg (Janssen Pharmaceutical K.K.), and others
 Trilafon Powder 1%, Trilafon Tablets 2 mg, 4 mg, 8 mg (Kyowa Pharmaceutical Industry Co., Ltd.)
 PZC Intramuscular Injection 2 mg (Mitsubishi Tanabe Pharma Corp.)
 PZC Intramuscular Powder 1% (Mitsubishi Tanabe Pharma Corp.)
 PZC Sugar-coated Tablets 2 mg, 4 mg, 8 mg (Mitsubishi Tanabe Pharma Corp.)
 Cremin Granules 10%, Cremin Tablets 10 mg, 25 mg, 50 mg (Mitsubishi Tanabe Pharma Corp.)

[Adverse reactions (clinically significant adverse reactions)]

Agranulocytosis, white blood cell decreased: Agranulocytosis and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

3 <Psychotropics>
Haloperidol decanoate

[Brand Name] Neoperidol Injections 50, 100 (Johnson & Johnson K.K.), Halomonth Injections 50 mg, 100 mg (Janssen Pharmaceutical K.K.)

[Adverse reactions (clinically significant adverse reactions)]

Agranulocytosis, white blood cell decreased: Agranulocytosis and white blood cell decreased may occur. If any abnormalities (such as pyrexia, pharyngeal pain, general malaise as initial symptoms) are observed, administration should be discontinued and a blood test should be performed.

<Psychotropics>
**4 Prochlorperazine maleate
 Prochlorperazine mesilate
 Propericiazine**

[Brand Name] Novamin Tablets 5 mg (Shionogi & Co., Ltd.)
 Novamin Intramuscular Injection 5 mg (Shionogi & Co., Ltd.)
 Neuleptil Fine Granule 10%, Neuleptil Tablets 5 mg, 10 mg, 25 mg, Neuleptil Oral Solution 1% (Shionogi & Co., Ltd.)

[Adverse reactions (clinically significant adverse reactions)]

Aplastic anaemia, agranulocytosis, white blood cell decreased: Aplastic anaemia, agranulocytosis and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, the dose should be reduced or administration should be discontinued.

<Psychotropics>
**5 Chlorpromazine hydrochloride
 Chlorpromazine hibenzate
 Chlorpromazine phenolphthalinate**

[Brand Name] Wintermin Tablets 12.5 mg, 25 mg, 50 mg, 100 mg (Shionogi & Co., Ltd.), Contomin Sugar-coated Tablets 12.5 mg, 25 mg, 50 mg, 100 mg, Contomin Intramuscular Injections 10 mg, 25 mg, 50 mg (Mitsubishi Tanabe Pharma Corp.)
 Contomin Powder 10%, Contomin Granule 10% (Mitsubishi Tanabe Pharma Corp.)
 Wintermin Fine Granule (10%) (Shionogi & Co., Ltd.)

[Adverse reactions (clinically significant adverse reactions)] Aplastic anaemia, haemolytic anaemia, agranulocytosis, white blood cell decreased: Aplastic anaemia, haemolytic anaemia, agranulocytosis, and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, the dose should be reduced or administration discontinued.

<Psychotropics>

6 Chlorpromazine hydrochloride/Promethazine hydrochloride/ Phenobarbital

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

[Adverse reactions (clinically significant adverse reactions)] Aplastic anaemia, haemolytic anaemia, platelets decreased, agranulocytosis, white blood cell decreased: Aplastic anaemia, haemolytic anaemia, platelets decreased, agranulocytosis, and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, the dose should be reduced or administration should be discontinued.

<Psychotropics>

7 Haloperidol

[Brand Name] Serenace Fine Granule 1%, Serenace Tablets 0.75 mg, 1 mg, 1.5 mg, 3 mg, Serenace Oral Solution 0.2%, Serenace for Injection 5 mg (Dainippon Sumitomo Pharma Co., Ltd.), and others

[Adverse reactions (clinically significant adverse reactions)] Agranulocytosis, white blood cell decreased: Agranulocytosis and white blood cell decreased may occur. If any abnormalities (such as pyrexia, pharyngeal pain, general malaise as initial symptoms) are observed, administration should be discontinued and a blood test should be performed.

<Psychotropics>

8 Levomepromazine hydrochloride Levomepromazine maleate

[Brand Name] Hirnamin Intramuscular Injection 25 mg (Shionogi & Co., Ltd.), Levotomin Intramuscular Injection 25 mg (Mitsubishi Tanabe Pharma Corp.), Hirnamin Fine Granules 10%, Hirnamin Powder 50%, Hirnamin Tablets (5 mg), (25 mg), (50 mg) (Shionogi & Co., Ltd.), Levotomin Powder 10%, 50%, Levotomin Granule 10 %, Levotomin Tablets 5 mg, 25 mg, 50 mg (Mitsubishi Tanabe Pharma Corp.), and others

[Adverse reactions (clinically significant adverse reactions)] Aplastic anaemia, agranulocytosis, white blood cell decreased: Aplastic anaemia, agranulocytosis, and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, the dose should be reduced or administration should be discontinued.

<Psychotropics>

9 Perospirone hydrochloride hydrate

[Brand Name] Lullan Tablets 4 mg, 8 mg, 16 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Important Precautions] Administration of this drug may cause hyperglycaemia or worsening of diabetes resulting in diabetic ketoacidosis or diabetic coma. During administration of this drug, caution should be exercised regarding the onset of symptoms such as thirst, polydipsia, polyuria, and pollakiuria. Patients, particularly those with a present or past history of diabetes mellitus, or with diabetic risk factors, should be carefully monitored, e.g. by measuring blood glucose levels.
Prior to initiation of the treatment with this drug, patients and their families should be given adequate information about the possibility of the occurrence of the above adverse reactions and to watch for abnormalities such as thirst, polydipsia, polyuria, and

pollakiuria. Patients should be instructed to discontinue the drug and consult a doctor immediately if such symptoms develop.

[Adverse reactions (clinically significant adverse reactions)]

Agranulocytosis, white blood cell decreased: Agranulocytosis and white blood cell decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

Hyperglycaemia, diabetic ketoacidosis, diabetic coma: Hyperglycaemia and worsening of diabetes may occur, resulting in diabetic ketoacidosis and diabetic coma. Caution should be paid to the onset of symptoms such as thirst, polydipsia, polyuria, pollakiuria, and patients should be carefully monitored e.g. by measuring blood glucose levels. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken, such as administration of insulin preparations.

<Antitussives, antitussives and expectorants>

**10 Dihydrocodeine phosphate/dl-Methylephedrine hydrochloride/
Chlorpheniramine maleate
Dihydrocodeine phosphate/Ephedrine hydrochloride/Ammonium
chloride/Platycodon fluid extract/Glycyrrhiza extract/Plantago herb
extract/Peony root extract/Dihydrocodeine phosphate**

[Brand Name] Huscode Combination Tablet, Huscode Combination Syrup (Abbott Japan Co., Ltd.), and others
Sekicode Combination Syrup (Dainippon Sumitomo Pharma Co., Ltd.)
Opisezol Codeine Powder, Opisezol Codeine Liquid (Nichi-Iko Pharmaceutical Co., Ltd.)

[Use in Pregnant, Parturient And Nursing Women] Nursing mothers should discontinue breast-feeding during treatment with this drug. [It has been reported that a similar compound of dihydrocodeine (codeine) was excreted in breast milk which resulted in morphine intoxication of the infant.]

<Antitussives>

**11 Diprophylline/Dihydrocodeine phosphate/dl-Methylephedrine
hydrochloride/Diphenhydramine
salicylate/Acetaminophen/Bromovalerylurea**

[Brand Name] Coughcode-N Combination Tablets (Mylan Seiyaku Ltd.)

[Use in Pregnant, Parturient And Nursing Women] Nursing mothers should discontinue breast-feeding during treatment with this drug. [It has been reported that a similar compound of dihydrocodeine (codeine) was excreted in breast milk which resulted in morphine intoxication in the infant. Animal studies in rats have shown that diphenhydramine is excreted in milk.]

<Antitussives and expectorants, Opium alkaloids>

**12 Codeine phosphate hydrate
Cherry bark extract/Codeine phosphate hydrate**

[Brand Name] Codeine Phosphate Hydrate “Shionogi” Codeine Phosphate Powder 10% “Shionogi”, Codeine Phosphate Tablet 20 mg “Shionogi” (Shionogi Co., Ltd.), Codeine Phosphate Hydrate “Daiichi Sankyo”, Codeine Phosphate Powder 10% “Daiichi Sankyo”, Codeine Phosphate Tablet 20 mg “Daiichi Sankyo” (Daiichi Sankyo Propharma Co., Ltd.), Codeine Phosphate Powder 1% “Daiichi Sankyo” (Daiichi Sankyo Co., Ltd.), Codeine Phosphate Hydrate “Takeda”, Codeine Phosphate Powder 10% “Takeda”, Codeine Phosphate Powder 1% “Takeda”, Codeine Phosphate Tablet 20 mg “Takeda” (Takeda Pharmaceutical Co., Ltd.), Codeine Phosphate “Tanabe”, Codeine Phosphate Powder 10% “Tanabe”, Codeine Phosphate Powder 1% “Tanabe” (Mitsubishi Tanabe Pharma Factory Ltd.), Codeine Phosphate Powder 10%, Codeine Phosphate Tablet (Dainippon Sumitomo Pharma Co., Ltd.)
Brocin-Codeine Combination Syrup, Concentrated (Daiichi Sankyo Co., Ltd.), and others

[Use in Pregnant, Parturient And Nursing Women]

Nursing mothers should discontinue breast-feeding during treatment with this drug. [It has been reported that the drug was excreted in breast milk which resulted in morphine intoxication in the infant.]

13

<Antitussives and expectorants, opium alkaloids>

Dihydrocodeine phosphate

[Brand Name]

Dihydrocodeine Phosphate “Shionogi”, Dihydrocodeine Phosphate Powder 10% “Shionogi” (Shionogi & Co. Ltd.), Dihydrocodeine Phosphate Powder 1% “Daiichi Sankyo” (Daiichi Sankyo Co., Ltd.), Dihydrocodeine Phosphate “Daiichi Sankyo”, Dihydrocodeine Powder 10% “Daiichi Sankyo” (Daiichi Sankyo Propharma Co., Ltd.), Dihydrocodeine Phosphate “Takeda”, Dihydrocodeine Phosphate Powder 10 % “Takeda”, 1% “Takeda” (Takeda Pharmaceutical Co., Ltd.), Dihydrocodeine Phosphate “Tanabe” (Mitsubishi Tanabe Pharma Factory Ltd.), and others

[Use in Pregnant, Parturient And Nursing Women]

Nursing mothers should discontinue breast-feeding during treatment with the drug. [It has been reported that a similar compound of dihydrocodeine (codeine) was excreted in breast milk which resulted in morphine intoxication in the infant.]

14

<Antivirals>

Etravirine

[Brand Name]

Intelence Tablets 100 mg (Janssen Pharmaceutical K.K.)

[Important Precautions]

The frequent occurrence of mild-to-moderate rash has been reported during administration of this drug. Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and severe rash including erythema multiforme have been reported in association with administration of this drug. If severe rash is observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

[Adverse reactions (clinically significant adverse reactions)]

Serious skin disorder: Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and hypersensitivity characterized by rash accompanied by erythema multiforme and general symptoms have been reported. Patients should be carefully monitored and if severe rash or rash accompanied by pyrexia, lymphadenopathy, hepatic function disorder or eosinophil count increased occur, administration of this drug should be discontinued immediately and appropriate measures should be taken.

<Over-the-counter drugs>

15

Preparations containing codeine phosphate hydrate Preparations containing dihydrocodeine phosphate Preparations containing hydrocodeine phosphate sekisanol

[Brand Name]

Aneton Cough Z Liquid (Johnson & Johnson), S.Tac EVE Tablets (SSP Co. Ltd.), Colgen Kowa Cough Liquid (Kowa Co. Ltd.), Neo Cough Medicine (Tenshindo Pharmaceutical Co., Ltd.), NESSHINGAN (Tanso Yakuhin Kogyo K.K.)

[When not to use the product]

Nursing mothers should not take this drug, or should discontinue breast-feeding when taking this drug.

[Consultation]

Delete “nursing mothers”.

4

List of products subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its Marketing Authorization Holder collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of January 1, 2010)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Infliximab (Genetical Recombination) ----- REMICADE for I.V. Infusion100* ¹	Mitsubishi Tanabe Pharma Corporation	July 7, 2009
Etanercept (Genetical Recombination) ----- ENBREL 25mg for S.C. Injection* ²	Wyeth K.K.	July 7, 2009
Somatropin (Genetical Recombination) ----- Growject injection 1.33mg, 8 mg, Growject bi-chamber 8mg* ³	JCR Pharmaceuticals Co., Ltd.	July 7, 2009
Follitropin Alfa (Genetical Recombination) ----- Gonalef 75, Gonalef Pen 450, 900* ⁴	Merck Serono Co., Ltd.	July 7, 2009
Levofloxacin Hydrate ----- CRAVIT TABLETS 250 mg, 500 mg, CRAVIT FINE GRANULES 10%	Daiichi Sankyo Company, Limited.	July 7, 2009
Clozapine ----- Clozaril Tablets 25 mg, 100 mg	Novartis Pharma K.K.	July 29, 2009
Tebipenem Pivoxil ----- ORAPENEM FINE GRANULES 10% FOR PEDIATRIC	Meiji Seika Kaisha, LTD.	August 26, 2009
Dutasteride ----- Avolve Capsules 0.5 mg	GlaxoSmithKline K.K.	September 4, 2009
Mirtazapine ----- RFLEX TABLETS 15 mg	Meiji Seika Kaisha, LTD.	September 7, 2009
Mirtazapine ----- Remeron tablets 15 mg	Schering-Plough K.K.	September 7, 2009
Mometasone Furoate ----- Asmanex Twisthaler 100 µg 60 doses	Schering-Plough K.K.	September 14, 2009
Aliskiren Fumarate ----- Rasilez Tablets 150 mg	Novartis Pharma K.K.	October 1, 2009
Bimatoprost ----- LUMIGAN OPHTHALMIC SOLUTION 0.03%	Senju Pharmaceutical Co., Ltd.	October 5, 2009
Paroxetine Hydrochloride Hydrate ----- PAXIL Tablets 10 mg, 20 mg* ⁵	GlaxoSmithKline K.K.	October 16, 2009
Interferon Beta -----	Toray Industries, Inc.	October 16, 2009

FERON Injections 1×10^6 IU, 3×10^6 IU, 6×10^6 IU ^{*6}		
Ribavirin REBETOL Capsules 200 mg ^{*7}	Schering-Plough K.K.	October 16, 2009
Voglibose BASEN Tablets 0.2, BASEN OD Tablets 0.2 ^{*8}	Takeda Pharmaceutical Company Limited	October 19, 2009
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL, 400 mg/16 mL Intravenous Infusion ^{*9}	Chugai Pharmaceutical Co., Ltd.	November 6, 2009
Amlodipine Besilate/Atorvastatin Calcium Hydrate Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban	Pfizer Japan Inc.	December 2, 2009
Sitagliptin Phosphate Hydrate GLACTIV Tablets 25 mg, 50 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	December 11, 2009
Sitagliptin Phosphate Hydrate JANUVIA Tablets 25mg, 50 mg, 100 mg	Banyu Pharmaceutical Co., Ltd.	December 11, 2009
Tadalafil Adcirca Tablets 20 mg	Eli Lilly Japan K.K.	December 11, 2009
Dexamethasone Cipeclate Erizas Capsule for Nasal Spray 400 µg	Nippon Shinyaku Co., Ltd.	December 11, 2009
Mesalazine ASACOL Tablets 400 mg	Zeria Pharmaceutical Co., Ltd.	December 16, 2009
Etanercept (Genetical Recombination) ENBREL 10mg for S.C. Injection	Wyeth K.K.	December 17, 2009
Recombinant Absorbed Bivalent Human Papillomavirus-like Particle Vaccine (derived from Trichoplusia ni cells) Cervarix	GlaxoSmithKline K.K.	December 22, 2009
Vancomycin Hydrochloride Vancomycin Ophthalmic Ointment 1%	Toa Pharmaceutical Co., Ltd.	December 28, 2009

*1: An additional indication for “treatment of patients with rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention of structural damage to joints)”

*2: An additional indication for “treatment of patients with polyarticular-course juvenile idiopathic arthritis (only for cases not adequately responsive to conventional therapies)”

*3: An additional indication for “treatment of patients with adult growth hormone deficiency (restricted to serious cases)”

*4: An additional indication for “ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders or polycystic ovarian syndrome”

*5: An additional indication for “treatment of patients with social anxiety disorder”

*6: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with ribavirin in patients either (1) with elevated blood HCV-RNA levels or (2) who did not respond to interferon monotherapy or relapsed after interferon monotherapy”

*7: An additional indication for “improvement of viremia associated with chronic hepatitis C in combination therapy with interferon beta in patients either (1) with elevated blood HCV-RNA levels or (2) who did not respond to interferon monotherapy or relapsed after interferon monotherapy”

*8: An additional indication for “inhibition of the development of type II diabetes mellitus in patients with abnormal glucose tolerance (only when diet and exercise therapies failed to improve the condition)”

*9: An additional indication for “treatment of patients with advanced or recurrent, inoperable non-squamous non-small cell lung cancer except for squamous cell carcinoma”