Pharmaceuticals and Medical Devices Safety Information

No. 223 March 2006

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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).

1

Important Safety Information

This section presents contents of revisions, reference materials, and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No.222).

1 Selegiline Hydrochloride

Brand Name (name of company)	FP Tablets-2.5 (FP Pharmaceutical Corporation)
Therapeutic Category	Antiparkinsonian agents
Indications	Concomitant therapy with levodopa-containing drug for the following diseases Parkinson's disease (sufficient efficacy has not been demonstrated with levodopa-containing drugs in the past treatment: Yahr Staging Scale I-Ⅳ)

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

[Adverse Reactions (clinically significant adverse reactions)

Neuroleptic malignant syndrome: Due to discontinuation or sudden reduction in the dosage of this drug, pyrexia, consciousness disturbed, severe muscle stiffness, movements involuntary, and serum CK (CPK) increased, etc. may occur. In such cases, the dose should be tapered after readministering this drug, and appropriate measures such as cooling of the body and fluid replacement, etc should be taken. Similar symptoms may also occur during continued administration of this drug.

Hypoglycaemia: Hypoglycaemia may occur. If symptoms of hypoglycaemia (consciousness disturbed and coma etc.) are observed, appropriate measure such as discontinuation of administration should be taken.

Gastric ulcer: Gastric ulcer may occur. In such cases, appropriate measures such as discontinuing treatment should be taken.

<Reference Information>

Company report
The number of related adverse reaction reports since the initial marketing (approximately 7 years)
(exclusive of "causality could be denied" and inclusive of "causality is unknown")

- Neuroleptic malignant syndrome: 4 cases (no fatal case)
- Hypoglycaemia: 3 cases (no fatal case)
- Gastric ulcer: 4 cases (no fatal case)

The number of patients treated with Selegiline for a year estimated by MAH (Marketing Authorisation Holder): approximately 32000 (2005)

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	Parkinson's disease (neuropathic bladder, hypertension)	2.5 mg 31 days	**Neuroleptic malignant syndrome** On day 1 of administration: Administration of this drug at 2.5 mg for Parkinson's disease was initiated. On day 29 of administration: Pyrexia and akinesia developed. On day 31 of administration (day of discontinuation): The patient was hospitalized, and she was diagnosed with neuroleptic malignant syndrome as CK (CPK) increased was confirmed. Discontinuation of this drug and initiation of fluid replacement, and dantrolene sodium were implemented. 14 days after discontinuation: The patient recovered.	Company report
	Concomitant medications: levodopa/carbidopa, ifenprodil tartrate, sennoside, magnesium oxide, propiverine hydrochloride, nilvadipine, oxybutynin hydrochloride				

Clinical Laboratory Values

	169 days before administration	On day 31 of administration (day of discontinuation)	14 days after discontinuation
BT (°C)	36.2	39.0	36.5
WBC (/mm^3)	8300	8600	7500
CK (CPK) (IU/L)	127	2269	118
AST (GOT) (IU/L)	31	73	45
ALT (GPT) (IU/L)	15	39	57
LDH (IU/L)	230	421	206
BUN (mg/dL)	26	36	18
Urinary protein (qualitative)	--	(2+)	--
Urinary occult blood (qualitative)	--	(3+)	--

BT: Body Temperature
WBC: White Blood Cell
CK (CPK): Creatine Kinase
AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase
LDH: Lactate Dehydrogenase
BUN: Blood Urea Nitrogen

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 80s	Parkinson's disease (hemorrhoids, gonarthrosis)	2.5 mg 279 days	**Hypoglycaemia** On day 1 of administration: Administration of this drug at 2.5 mg for Parkinson's disease was initiated. On day 227 of administration: Hypanakinesia was noted. On day 278 of administration: Consciousness disturbed occurred. On day 279 of administration (day of discontinuation): Blood glucose level in the morning was 100 mg/dL. In the evening, as rapid decrease in blood glucose level (40 - 96 mg/dL) and depressed level of consciousness were confirmed, the patient was hospitalized. The patient was in the state of delirium at the time of hospitalization. Administration of this drug and other oral antiparkinsonian agents were discontinued. The patient was treated with levodopa and glucose drip infusion. 1 day after discontinuation: Blood glucose level was 60 mg/dL. The patient became responsive to calling. 2 days after discontinuation: Blood glucose level was 57 - 64 mg/dL. 3 days after discontinuation: Blood glucose level was slightly recovered with 70 mg/dL. 5 days after discontinuation: Blood glucose level was 96 - 166 mg/dL. Oral intake became possible. 9 days after discontinuation: The patient recovered.	Company report
	Concomitant medications: levodopa/carbidopa, droxidopa, bromocriptine mesilate				

Clinical Laboratory Values

	On day 279 of administration (day of discontinuation)		1 day after discontinuation	2 days after discontinuation	3 days after discontinuation	5 days after discontinuation
	Morning	Evening				
Blood glucose level (mg/dL)	100	40 - 96	60	57 - 64	70	96 - 166

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
3	Male 70s	Parkinson's disease (lacunar infarction, chronic cardiac failure, hypertension, left inguinal hernia)	2.5 mg 28 days ↓ 5.0 mg 298 days	**Gastric ulcer** Red blood cell had been in the lower limit range of normal ($379 \times 10^4/mm^3$). On day 1 of administration: Administration of this drug at 2.5 mg for Parkinson's disease was initiated. On day 29 of administration: The dose of this drug was increased to 5.0 mg. On day 120 of administration: Red blood cell was $378 \times 10^4/mm^3$. Approx. on day 290 of administration: Anaemia and weight decreased developed. On day 302 of administration: Red blood cell $328 \times 10^4/mm^3$, haemoglobin 11.0 g/dL, and body weight −5 kg/month. On day 326 of administration (day of discontinuation): Gastric ulcer (perforation) developed. The patient was emergently hospitalized due to pre-shock. Administration of this drug was discontinued. 113 days after discontinuation: The patient recovered.	Company report
	Concomitant medications: aspirin/dialuminate for children, levodopa/carbidopa, trihexyphenidyl hydrochloride, amantadine hydrochloride, ubidecarenone				

Clinical Laboratory Values

	Prior to administration	On day 120 of administration	On day 302 of administration
RBC ($\times 10^4/mm^3$)	379	378	328
Hb (g/dL)	--	--	11.0

RBC: Red Blood Cell Hb: Haemoglobin

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Revision of PRECAUTIONS

(No. 174)

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

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1 <Antipyretics and analgesics, anti-inflammatory agents>
Lornoxicam

[Brand Name] Lorcam Tab. 2 mg and 4 mg (Taisho Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Peptic ulcer, small intestine ulcer, large intestinal ulcer (all possibly complicated by bleeding and/or perforation):** Since peptic ulcer, small intestine ulcer, and/or large intestinal ulcer without perforation (or possibly with perforation) may occur, patients should be carefully monitored. If abnormalities (abdominal pain, vomiting, or gastrointestinal haemorrhage with haematemesis, melaena, and/or the like) are observed, administration should be discontinued, and appropriate measures should be taken.

<Reference Information> Company report

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2 <Acting mainly on gram-positive bacteria and gram-negative bacteria>
Ceftazidime

[Brand Name] Modacin for Injection (GlaxoSmithKline K.K.) and others

[Adverse Reactions (clinically significant adverse reactions)] Pancytopenia, agranulocytosis, haemolytic anaemia, and platelets decreased may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

<Reference Information> Company report

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3 <Anthelmintics>
Albendazole

[Brand Name] Eskazole Tablets (GlaxoSmithKline K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme:** Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme may occur. Patients should be carefully monitored and if abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

4 <Over the counter drugs> Bacitracin/Fradiomycin Sulfate/Hydrocortisone Acetate

[Brand Name] Dolmycorti Ointment (Zeria Pharmaceutical Co., Ltd.)

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

In rare instances, the following serious symptoms may occur. In this case, receive immediate examination by a physician.

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

<Reference Information> Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of March 1, 2006)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Doripenem Hydrate / Finibax 0.25 g IV Solution	Shionogi & Co., Ltd.	September 16, 2005
Dehydrated Ethanol / Anhydrous Ethanol Injection "Fuso"	Fuso Pharmaceutical Industries, Ltd.	September 16, 2005
Dehydrated Ethanol / Dehydrated Ethanol Inj. "Merck"	Merck Hoei Ltd.	September 20, 2005
Pilocarpine Hydrochloride / Salagen Tab. 5 mg	Kissei Pharmaceutical Co., Ltd.	September 22, 2005
Gemtuzumab Ozogamicin (Genetical recombination) / Mylotarg Injection 5 mg	Wyeth K.K.	September 22, 2005
Alteplase (Genetical recombination) / Activacin for Injection 6000000, 12000000, and 24000000[*1]	Kyowa Hakko Kogyo Co., Ltd.	October 11, 2005
Alteplase (Genetical recombination) / Grtpa Inj. 6000000, 12000000, and 24000000[*1]	Mitsubishi Pharma Corporation	October 11, 2005
Candesartan Cilexetil / Blopress Tablets 2, 4, and 8[*2]	Takeda Pharmaceutical Company Limited	October 11, 2005
Moxifloxacin Hydrochloride / Avelox Tablets 400 mg	Bayer Yakuhin, Ltd.	December 9, 2005
Finasteride / Propecia Tablets-0.2 mg and 1 mg	Banyu Pharmaceutical Co., Ltd.	December 14, 2005
Miglitol / Seibule Tab. 25 mg, 50 mg, and 75 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	January 11, 2006
Potassium Clavulanate/Amoxicillin / Clavamox Dry Syrup for Pediatric	GlaxoSmithKline K.K.	January 17, 2006
Paroxetine Hydrochloride Hydrate / Paxil Tablets 10 mg and 20 mg[*3]	GlaxoSmithKline K.K.	January 23, 2006
Ciclosporin / Papilock Mini Ophthalmic Solution 0.1%	Santen Pharmaceutical Co., Ltd.	January 23, 2006

Placental Gonadotrophin Profasi Injection 5000[*4]	Serono Japan Co., Ltd.	January 30, 2006
Zanamivir Hydrate Relenza[*5]	GlaxoSmithKline K.K.	February 17, 2006

Note) Subject to additional indications etc.

*1: An additional indication for "the improvement of dysfunction in the acute stage of ischemic cerebrovascular disease (within 3 hours of onset)"

*2: An additional indication for "the treatment of patients in the condition of chromic cardiac failure (mild to moderate) for which administration of angiotensin converting enzyme (ACE) inhibitors is not appropriate"

*3: An additional indication for "obsessive-compulsive disorder"

*4: An additional indication for "induction of spermatogenesis in hypogonadotropic male hypogonadism"

*5: An additional administration for "pediatrics"