Pharmaceuticals and Medical Devices Safety Information

No. 228 September 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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No. 228 September 2006

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

[Outline of Information]

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

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

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

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Reports etc. on adverse reactions associated with influenza vaccines in FY 2005

(1) Introduction

Reports on adverse reactions associated with the influenza vaccines since FY 2003 have been described in the Pharmaceuticals and Medical Devices Safety Information No. 205 and No. 217. This section represents a summary of the reporting status and safety measures for adverse reactions associated with the influenza vaccines in FY 2005.

(2) Reporting status of adverse reactions associated with influenza vaccine in FY 2005

Estimated amount of shipment of the influenza vaccines in FY 2005 was approximately 19.32 million vials. Marketing authorisation holders etc. reported 102 cases and 139 events, including those for which causality with the pharmaceutical is unknown, as adverse reactions associated with the influenza vaccination in accordance with Article 77-4-2, Paragraph 1 of the Pharmaceutical Affairs Law.

Major adverse reactions reported were 14 cases of hepatic function disorder, 11 cases of rash, 10 cases of shock/anaphylactoid symptoms, 10 cases of pyrexia, 9 cases of erythema/swelling of the injection site, 7 cases of convulsion and 4 cases of Guillain-Barre syndrome etc..

Table 1 indicates the reporting status of adverse reactions associated with influenza vaccine, according to the number of cases per age group and outcome.

In addition, as for reported cases of death and cases with sequelae, the results of a review by the vaccine adverse reaction review committee formed from specialists in infectious diseases and viruses (hereinafter referred to as “vaccine adverse reaction review committee”) are shown in **Table 2** and **3,** respectively.

Aside from reports on adverse reactions based on the Pharmaceutical Affairs Law, a Vaccine Adverse Reaction Reporting System was established in accordance with amendments to the Preventive Vaccinations Law in 1994. For reference, **Table 4** indicates the number of adverse reactions reported from influenza vaccination (reported regardless of causality) in FY 2005 through this system. The Vaccine Adverse Reaction Reporting System is intended based on Immunization Practices for collecting the information of change in health conditions of the vaccinated individuals by the Preventive Vaccination Law, providing the public a broad range of information, where the individuals subject to the system are limited only to the target of routine vaccination and differ from individuals targeted for reports on adverse reactions, etc. in accordance with the Pharmaceutical Affairs Law.

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Table 1 The number of reported status of adverse reactions associated with influenza vaccination in FY 2005

Age Group	Total		Recovery/ Remission		Unrecovered		Unknown		Sequelae		Death	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	102		74		7		14		4 (4)		0 (3)	
	41	61	33	41	3	4	4	10	1 (1)	3 (3)		0 (3)
Under age of 10	33		25		3		3		2 (2)			
	17	16	13	12	2	1	1	2	1 (1)	1 (1)		
10s	13		12								0 (1)	
	6	7	6	6								0 (1)
20s	7		5				1		1 (1)			
	2	5	2	3				1		1 (1)		
30s	6		5		1							
	3	3	3	2		1						
40s	12		8		1		3					
	4	8	3	5	1			3				
50s	4		3				1					
	2	2	2	1				1				
60s	6		4				2					
	1	5	1	3				2				
70s	11		6		1		2		1 (1)		0 (1)	
	3	8	1	5		1	2			1 (1)		0 (1)
80s	8		6				1				0 (1)	
	2	6	2	4				1				0 (1)
90s	2				1		1					
	1	1				1	1					

(Notes) As for sequelae and death, the number of cases where causality between the reported adverse reactions and influenza vaccination could not be denied is indicated; the numbers inside the ( ) include all reported cases, including those for which a causality is not established. With regard to recovery/remission, unrecovered, and unknown, the number of all reported cases are shown regardless of causality.

Table 2 Cases of death associated with influenza vaccination in FY 2005

No.	Case summary	Evaluation by experts
1	Female in 70s Name of adverse reaction: hepatic failure (acute hepatic failure) Past history/complications: unremarkable The patient received influenza vaccination. Afterwards, pyrexia, vomiting, queasy, and difficulty eating were repeated, and acute hepatic failure was developed. The patient was hospitalized 71 days after vaccination. Hepatosplenomegaly, gallstones, and cholecystitis were confirmed in echo, and pleural effusion and ascites were increased. The patient died 130 days after vaccination.	Since there is no detailed information such as clinical symptoms and clinical laboratory values from when the influenza vaccine was inoculated until hepatic failure was manifested, the causality with influenza vaccination is unevaluable.
2	Female in 80s Name of adverse reaction: encephalitis Past history/complications: chronic renal failure, multiple cerebral infarction (occurred 16 days before vaccination), asthma bronchial, somnolence The patient received influenza vaccination. 1 day after vaccination, pyrexia, redness of eyelid, and itching developed.	The findings lacked evidence to support the diagnosis of encephalitis. It was considered that aggravation of multiple cerebral infarction that had developed before vaccination occurred. The causality with influenza vaccination cannot be established.

	2 days after vaccination, vomiting, wheezing, and movements involuntary around the neck appeared. In a head MRI, a line-like infarction in the right cerebellum, and small infarctions around the lateral ventricle/occipital lobe were observed. 13 days after vaccination, treatment with antimicrobial drugs and non-pyrazolone cold drug was initiated due to white blood cell increased and CRP increased. 15 days after vaccination, the patient was diagnosed with encephalitis based on an MRI and electroencephalogram, and treatment with steroids was initiated. 51 days after vaccination, the patient died.	
3	Female in 10s Name of adverse reaction: myocarditis (acute myocarditis) Past history/complications: dermatitis atopic, anaemia, pacemaker generated rhythm The patient received the second influenza vaccination. Later, the patient developed pyrexia of 38.8°C. 1 day after vaccination, the patient received consultation from local physician A, and was diagnosed with a common cold. Treatment with general cold medicine, antibiotics, and anti-inflammatory agents, etc. was initiated. 2 days after vaccination, although pyrexia abated, the patient had strong general malaise and chest pain, and received consultation from local physician B. Patient had difficulty walking independently, and hypotension and cardiac function failed were confirmed. Afterwards, the patient was transferred to hospital C due to suspicion of cardiogenic shock. Ventricular pacing was initiated for atrioventricular block complete, but ventricular fibrillation developed. 3 days after vaccination, the patient died.	Since the development of symptoms occurred within 12 hours after the second vaccination, a causality cannot completely be denied based on the time course, but since information such as clinical laboratory values and autopsy results, which are necessary when reviewing the cause of acute myocarditis, have not been obtained, as a comprehensive evaluation, causality with influenza vaccination is unevaluable.

(Reference) Cases of death by influenza vaccination in FY 2005 that were reported in FY 2006

No.	Case summary	Evaluation by experts
1	Female in 80s Name of adverse reaction: sudden death Past history/complications: hypertension The patient received influenza vaccination. The patient's body temperature was 36.8°C at the time of vaccination, and there were no abnormal findings in the patient's condition. According to her family members, even afterwards, there were no particular changes. 6 days after vaccination, her family members found the patient collapsed in the bathroom. The patient was sent to the hospital, but died.	As there is insufficient information, such as a lack of detailed information regarding the past history and conditions leading to the patient's death, a causality with influenza vaccination is unevaluable.
2	Male in 60s Names of adverse reactions: pulmonary oedema, pneumonia Past history/complications: hypertension The patient received influenza vaccination**.** (date of vaccination etc. unknown) The patient fell into pain suddenly, and made emergency outpatient visit to hospital. Depressed	As there is insufficient information, such as a lack of detailed information regarding the time from vaccination until the onset of symptoms, a causality with influenza vaccination is unevaluable.

	level of consciousness and unrest were noted. The patient was in a condition with marked hypoxemia, hypercapnia, and acidosis. In an auscultation of the chest, moist rales were heard. Chest X-ray confirmed permeability loss in both lungs. White blood cell count increased and CRP increased were noted. Artificial respiratory control was initiated, and even though acidosis was corrected, the patient underwent cardio-respiratory arrest 1 hour after coming to the hospital. Although heart started beating once after a cardiac massage etc., cardio-respiratory arrest occurred again. The patient died afterwards.	

Table 3 Cases with sequelae associated with influenza vaccination in FY 2005

No.	Case summary	Evaluation by experts
1	Male under the age of 10 Name of adverse reaction: encephalopathy (acute encephalopathy) Past history/complications: febrile convulsion The patient had received influenza vaccinations twice the year before the vaccination this year. But the patient had experienced no abnormalities such as side reactions. The patient received influenza vaccination. 3 hours after vaccination, convulsive seizure and pyrexia developed. The patient was sent to hospital by emergency services. Treatment with anticonvulsant, osmotic diuretic, antibiotics, etc. was initiated. Although convulsion disappeared, consciousness did not recover and a test on cerebrospinal fluid was conducted. (number of cells: 2/3, bacterial culture: negative, viral isolation: negative) 1 day after vaccination, hypothermia therapy and high dose immunoglobulin therapy were initiated. 48 days after vaccination, the patient was bedridden and had strong muscle tightness. The condition where patient could not make eye contact continued. Tube feeding and rehabilitation continued.	Although the patient has a past history of febrile convulsion, since he developed pyrexia and convulsion 3 hours after vaccination, and developed encephalopathy afterwards, a causality with influenza vaccination cannot be denied.
2	Female under age of 10 Name of adverse reaction: injection site scar Past history/complications: unremarkable Since 3 years ago, redness and swelling were observed at injection site when patient received influenza vaccination. Every year, the patient orally took antihistamines. The patient received the first influenza vaccination. 5 to 6 hours after vaccination, transient pyrexia and local reaction developed, similarly to the previous year. The patient received the second influenza vaccination. 5 to 6 hours after vaccination, hyperthermia of over 39°C and local swelling developed. 4 days after vaccination, pyrexia abated, but induration of 5.5 × 4.0 cm persisted at injection site, and the center of the site 2.0 ×1.5 cm became ulcerated. 9 days after vaccination, the center of the site became scarred.	Since the patient develops redness and swelling every year since 3 years ago, a causality with influenza vaccination is demonstrated.

3	Female in 70s Name of adverse reaction: Guillain-Barre syndrome Past history/complications: reflux oesophagitis, hypertension The patient received influenza vaccination. 27 days after vaccination, tingling sensation on both plantars developed. 30 days after vaccination, the patient was hospitalized at a local hospital. (cerebrospinal fluid examination was nearly normal) 32 days after vaccination, consciousness was lucid and there was no dyslalia. Lasegue's test positive, tendon reflex absent. The patient was in a bedridden condition, and was diagnosed with Guillain-Barre syndrome based on the findings of acute polyradiculoneuritis etc. 33 days after vaccination, bulbar palsy developed. Treatment with sulfonated human normal immunoglobulin G initiated. 46 days after vaccination, the patient was somewhat improved, and she was able to maintain after herself independently with some aid. 50 days after vaccination, the patient was transferred to another hospital for the purpose of continuing rehabilitation.	As symptoms developed within 1 month after vaccination, and there are no other causes that would result in neurotic diseases, a causality with influenza vaccination cannot be denied.
4	Female in 20s Name of adverse reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: unremarkable The patient received influenza vaccination. 7 days after vaccination, cold symptoms including pyrexia (37.4°C) developed. Furthermore, muscle weakness lower limb and dysuria were confirmed afterwards. 12 days after vaccination, the patient received consultation from local physician A due to dysuria. 15 days after vaccination, the patient received diagnosis at hospital B due to abasia and was hospitalized. Muscle weakness lower limb, decreased sensation in both legs, vesicorectal disorder were noted. High signal was confirmed between thoracic spine and thoracic segments in MRI of thoracic spine, and since cerebrospinal fluid cell count had also increased, the patient was diagnosed with ADEM and steroid pulse therapy was performed. 65 days after vaccination, a recovery tendency of symptoms was observed, but bladder disorder, muscle weakness lower limb and sensory disturbance persisted.	The patient developed common cold symptoms 1 week after vaccination, developed neurological symptoms by around the 2 weeks after vaccination, and was diagnosed with acute disseminated encephalomyelitis. Since there appear to be no other causes that would result in neurological symptoms, a causality with influenza vaccination cannot be denied.

Table 4 Reports of adverse reactions associated with influenza vaccines in FY 2005 (reported regardless of causality)

	Total	Recovery	Death	Serious	Hospitaliza-tion	Sequelae	Others	N/A
Total	58		3		14	1	17	23
1. Immediate systemic reaction	3				2		1	
1A. Anaphylaxis	2				2			
1B. Systemic urticaria	1						1	
2. Encephalitis, encephalopathy								
3. Convulsion								
4. Movement disorder	4				2	1		1
5. Other nerve disorders	4				1		1	2
6. Local abnormal swelling (over elbows)	1							1
7. Rash generalized	9						5	4
8. Pyrexia of 39°C and higher	11				4		2	5
9. Other abnormal reactions	9				2		4	3
10. Nonstandard reports	17		3		3		4	7
10A. Local reaction (redness and swelling etc.)	3						1	2
10B. Systemic reaction (pyrexia etc.)	10				2		3	5
10C. Others	4		3		1			

(3) Safety measures for influenza vaccination

Based on a review by the vaccine adverse reaction review committee, there were no adverse reactions etc. that need the discussion about new safety measures.

2

Revision of PRECAUTIONS

(No. 179)

This section presents details of the 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. 227), together with reference materials.

1 <Antiarrhythmic agents> Amiodarone Hydrochloride

[Brand Name]	Ancaron Tablets 100 (Sanofi-Aventis K.K.) and others
[Adverse Reactions (clinically significant adverse reactions)]	**Syndrome inappropriate ADH (SIADH):** Syndrome inappropriate ADH (SIADH) may occur. If symptoms such as hyponatraemia associated with blood hyposmosis, increased sodium excretion into the urine, convulsion and consciousness disturbed occur, administration should be discontinued and appropriate measures such as restricting fluid intake should be taken.
<Reference Information>	Company report

2 <Urogenital and anal organ agents-Miscellaneous> Silodosin

[Brand Name]	Urief Cap. 2 mg and 4 mg (Kissei Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Syncope, loss of consciousness:** Temporary loss of consciousness associated with blood pressure decreased 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

3 <Miscellaneous metabolism agents> Camostat Mesilate

[Brand Name]	Foipan Tablets 100 mg (Ono Pharmaceutical Co., Ltd.) and others
[Adverse Reactions (clinically significant adverse reactions)]	**Hyperkalaemia:** Serious hyperkalaemia may occur. Patients should be carefully monitored by conducting serum electrolyte tests etc. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

<Acting mainly on gram-positive bacteria and mycoplasma>

4 Telithromycin

[Brand Name] Ketek Tablets 300 mg (Sanofi-Aventis K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis, hepatic function disorder, jaundice: Hepatitis, hepatic function disorder with a significant increase in AST (GOT), ALT (GPT), and Al-P levels, etc, jaundice may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

QT prolongation: QT prolongation may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Chemotherapeutics-Miscellaneous>

5 Itraconazole

[Brand Name] Itrizole Capsules 50 (Janssen Pharmaceutical K.K.) and others

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), dermatitis exfoliative: Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), dermatitis exfoliative (erythroderma) may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Anaphylactoid symptoms: Anaphylactoid symptoms may occur. Patients should be carefully monitored, and if cyanosis, cold sweat, blood pressure decreased, dyspnoea and anxiety of the breast are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

<Human blood preparations>

6 Polyethylene Glycol Treated Human Normal Immunoglobulin

[Brand Name] Kenketsu Venoglobulin-IH Yoshitomi (Benesis Corporation) and others

[Contraindications]

Patients with hereditary fructose intolerance [Since D-sorbitol, the additive in this drug, metabolized to fructose is not metabolized normally, leading to the development of hypoglycaemia, etc., which may induce hepatic failure and renal failure.]

<Reference Information> Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of September 1, 2006)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Baclofen Intrathecal Gabalon 0.005%, 0.05%, and 0.2%	Daiichi Pharmaceutical Co., Ltd.	April 1, 2006
Interferon Beta Feron[*1]	Toray Industries, Inc.	April 20, 2006
Epoetin Beta (Genetical recombination) Epogin Injection Ampoule 750, 1500, and 3000, Epogin Injection Syringe 750, 1500, and 3000[*2]	Chugai Pharmaceutical Co., Ltd.	April 20, 2006
Somatropin (Genetical recombination) Humatrope C 6 mg and 12 mg[*3]	Eli Lilly Japan K.K.	April 20, 2006
Zoledronic Acid Hydrate Zometa Injection 4 mg[*4]	Novartis Pharma K.K.	April 20, 2006
Micafungin Sodium Funguard 50 mg and 75 mg for Infusion[*5]	Astellas Pharma Inc.	April 20, 2006
Linezolid Zyvox Tablets 600 mg, Zyvox Injection 600 mg[*6]	Pfizer Japan Inc.	April 20, 2006
Tosufloxacin Tosilate Tosuflo Ophthalmic Solution 0.3%	Nidek Co., Ltd.	April 28, 2006
Clopidogrel Sulfate Plavix Tablets 25 mg and 75 mg	Sanofi-Aventis K.K.	May 8, 2006
Silodosin Urief Cap. 2 mg and 4 mg	Kissei Pharmaceutical Co., Ltd.	May 11, 2006
Tosufloxacin Tosilate Ozex Ophthalmic Solution 0.3%	Toyama Chemical Co., Ltd.	May 11, 2006
Follitropin Alfa (Genetical recombination) Gonalef for S.C. Injection 75 and 150	Serono Japan Co., Ltd.	May 11, 2006
Letrozole Femara Tablets 2.5 mg	Novartis Pharma K.K.	May 11, 2006
Loxoprofen Sodium Loxonin PAP 100 mg	Lead Chemical Co., Ltd.	May 23, 2006
Aripiprazole Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%	Otsuka Pharmaceutical Co., Ltd.	June 8, 2006
Solifenacin Succinate Vesicare Tablets 2.5 mg and 5 mg	Astellas Pharma Inc.	June 8, 2006
Tolterodine Tartrate Detrusitol Capsules 2 mg and 4 mg	Pfizer Japan Inc.	June 8, 2006
Amphotericin B AmBisome for Intravenous Infusion 50 mg	Dainippon Sumitomo Pharma Co., Ltd.	June 20, 2006

Magnesium Sulfate/Glucose Magsent Injection 100 mL	Toa Pharmaceuticals Co., Ltd.	June 20, 2006
Sertraline Hydrochloride Jzoloft Tablets 25 mg and 50 mg	Pfizer Japan Inc.	July 7, 2006
Somatropin (Genetical recombination) Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg[*7]	Pfizer Japan Inc.	July 26, 2006
Inulin Inulead Inj.	FUJIYAKUHIN Co., Ltd.	August 22, 2006

Note: Subject to additional indication etc.

*1: An additional indication for "improvement of viraemia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA load)"

*2: An additional indication for "anaemia of prematurity"

*3: An additional indication for "adult growth hormone hyposecretion (for severe cases only)"

*4: An additional indication for "bone lesions due to multiple myeloma and solid tumor metastases to bone"

*5: An additional administration for "pediatrics"

*6: An additional indication for "<Susceptible strains> methicillin-resistant Staphylococcus aureus (MRSA) sensitive to this drug <Indications> sepsis, deep skin infection, chronic pyoderma, secondary infection such as from traumatic injury/fever and surgical wound, and pneumonia"

*7: An additional indication for "adult growth hormone hyposecretion (for severe cases only)"