Pharmaceuticals and Medical Devices Safety Information

No. 240 September 2007

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

Published by
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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. 240 September 2007

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	**Reports etc. on adverse reactions associated with influenza vaccines in FY 2006**	*C*	A summary of the reporting status etc. on adverse reactions associated with the influenza vaccine in FY 2006 will be presented. The estimated amount of consumption of the influenza vaccines in FY 2006 was approximately 18.77 million vials. Moreover, there were 107 cases and 149 events reported as adverse reactions etc. in accordance with the Pharmaceutical Affairs Law. Major adverse reactions consisted of 20 events of acute disseminated encephalomyelitis (leukoencephalomyelitis), 11 events of pyrexia, 8 events of rash etc., 8 events of erythema/swelling etc. of the injection site, 7 events of hepatic function disorder etc, 7 events of shock/anaphylactoid symptoms, 6 events of convulsion, and 4 events of Guillain-Barre syndrome etc.	3
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D: Distribution of Dear Healthcare Professional Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

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

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

1

Reports etc. on adverse reactions associated with influenza vaccines in FY 2006

(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, No. 217 and No. 228. This section represents a summary of the reporting status etc. on adverse reactions associated with the influenza vaccines in FY 2006.

(2) Reporting status of adverse reactions associated with influenza vaccines in FY 2006

Estimated amount of consumption of the influenza vaccines in FY 2006 was approximately 18.77 million, vials. Marketing authorisation holders etc. reported 107 cases and 149 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. **Table 1** indicates estimated amount of consumption, case number of reported adverse reactions, and event number of adverse reactions reported in the past 4 years, and **Table 2** for the reporting status of adverse reactions associated with influenza vaccination in FY 2006, according to the number of cases per age group, gender, and outcome.

Major adverse reactions reported in FY 2006 consisted of 20 events of acute disseminated encephalomyelitis (leukoencephalomyelitis), 11 events of pyrexia, 8 events of rash etc., 8 events of erythema/swelling etc. of the injection site, 7 events of hepatic function disorder etc., 7 events of shock/anaphylactoid symptoms, 6 events of convulsion, and 4 events of Guillain-Barre syndrome etc. From among these reports, while the numbers of reported adverse reactions of acute disseminated encephalomyelitis per fiscal year were 6 events, 4 events, and 20 events in FY 2004, FY 2005, and FY 2006, respectively, annual incidence of the adverse reaction was 9 events, 11 events, and 7 events in FY 2004, FY 2005, and FY 2006, respectively, which indicated no marked changes in the past 3 years.

In addition, as for reported cases of death and cases with sequelae in FY 2006, its summaries and the results of a review by the vaccine adverse reaction review committee formed from specialists in infectious diseases and viruses are shown in **Tables 3 and 4,** respectively.

Based on the result of a review by the vaccine adverse reaction review committee, the need to discuss new safety measures regarding the aforementioned points was not confirmed.

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 Vaccination Law in 1994. This 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. **Table 5** indicates the number of adverse reactions reported from influenza vaccination (reported regardless of causality) in FY 2006.

Table 1 Estimated amount of influenza vaccine consumption, number of reported adverse reaction cases, and number of adverse reactions reported in the past 4 years

	FY 2003	FY 2004	FY 2005	FY 2006
Estimated amount of consumption	Approximately 14.63 million vials	Approximately 15.98 million vials	Approximately 19.32 million vials	Approximately 18.77 million vials
Number of reported adverse reaction cases	162 cases	113 cases	102 cases	107 cases
Number of adverse reactions reported	259 events	205 events	139 events	149 events

Table 2 The number of reported adverse reaction cases associated with influenza vaccination per age group, gender, and outcome

Age group	Total		Recovery/ Remission		Unrecovered		Unknown		Sequelae		Death	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	107		72		5		17		8 (5)		5 (0)	
	51	56	32	40	3	2	9	8	3 (2)	5 (3)	4 (0)	1 (0)
Under age of 10	32		23		1		7		1 (0)			
	18	14	12	11	1		4	3	1 (0)			
10s	13		7				2		4 (4)			
	9	4	5	2			2		2 (2)	2 (2)		
20s	7		4		1		2					
	1	6	1	3		1		2				
30s	4		4									
	1	3	1	3								
40s	4		4									
	3	1	3	1								
50s	12		6				3		3 (1)			
	4	8	2	4			2	1		3 (1)		
60s	14		8		2		2				2 (0)	
	5	9	1	7	1	1	1	1			2 (0)	
70s	13		11		1						1 (0)	
	9	4	7	4	1						1 (0)	
80s	8		5				1				2 (0)	
	1	7		5				1			1 (0)	1 (0)

(Notes) 1. As for "Sequelae" and "Death," the number of cases where the causality between the reported adverse reaction and influenza vaccination could not be denied is indicated in ( ).

2. Duplicate counting when reported by multiple companies. Therefore, the number of reported cases differs from that of Table 4.

Table 3 Death case summary etc.

No.	Case summary	The result of a review by the study group
1	Female in 80s Name of adverse reaction: myocardial infarction Past history/complications: appendicectomy and hypertension The patient received influenza vaccination. Body temperature was 36.8°C at the time of vaccination. There were no abnormal findings in the patient's condition. According to family members, even afterwards, there were no particular changes. 6 days after vaccination, family members found the patient collapsed in the bathroom. The patient was sent to the hospital, but she died.	As there is insufficient information, such as lack of detailed information regarding the patient's past history and regarding the conditions leading to the patient's death, the causality between the event and the influenza vaccination cannot be assessed.
2	Male in 60s Name of adverse reaction: pulmonary oedema and pneumonia Past history/complications: hypertension The patient received influenza vaccination. There were no particular problems after the vaccination. 2 days after the vaccination, the patient fell into pain suddenly in the midnight, and made emergency outpatient visit to the hospital. Decreased level of consciousness and unrest were found. The patient was in a condition with marked hypoxemia, hypercapnia, and acidosis. In an auscultation of the chest, moist rales were heard. Permeability loss in both lungs was found in chest X-ray. WBC and CRP were increased. Artificial respiratory control was initiated. Even though the patient recovered from acidosis, he suffered 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.	As there is insufficient information, such as lack of detailed information regarding the time from the vaccination until the onset of symptoms, this case cannot be assessed as having a causality with inoculation of the influenza vaccine.
3	Male in 60s Name of adverse reaction: cardio-respiratory arrest, hypoglycemia, and leukopenia Past history/complications: chronic renal failure, chronic glomerulonephritis, angina pectoris, myocardial infarction, and pelvic fracture 14 years ago, chronic glomerulonephritis was developed. 8 years ago, haemodialysis was initiated. The patient received influenza vaccination on haemodialysis. No particular changes were observed after the vaccination. 2 days after vaccination, haemodialysis was conducted. There were symptoms of diarrhoea. No clear tenderness was observed. Levofloxacin, lactobacillus acidophilus preparation, and loperamide hydrochloride were administered. 4 days after vaccination, haemodialysis was conducted. 7 days after vaccination, there were no remarkable pyrexia and abdominal pain. Malaise was observed. Haemodialysis was conducted. Diarrhoea was improved. 8 days after vaccination, the patient was snoring at home in the evening. Later family members found that he was not breathing. They called an	This is a case of sudden death occurred 8 days after the vaccination of which was likely due to septic shock, leukopenia, and hypoglycemia. As the patient was treated with a long-term haemodialysis and the underlying diseases may have been the cause of death, the causality with influenza vaccine cannot be established.

	ambulance. Although cardiopulmonary resuscitation was started, the patient was unresponsive and died. Shock, leukopenia, and hypoglycemia were noted at the time of admission. Although blood culture was not conducted, sepsis was suspected from the patient's clinical conditions. After his death, the CT confirmed no clear haemorrhage, etc. in head, abdomen, or chest. Chest CT confirmed mild infiltrative shadows in both lungs. There were no autopsy findings.	
4	Male in 70s Name of adverse reaction: pyrexia Past history/complications: schizophrenia, constipation, insomnia, Parkinsonism, and agitation The patient received influenza vaccination. The patient had pyrexia of 37.7°C on the day of vaccination. 5 days after vaccination, pyrexia of 39.6°C was developed again. Diclofenac sodium suppository was used. Pyrexia was abated to 36.7°C. 8 days after vaccination, the patient had pyrexia of 39.2°C. Diclofenac sodium suppository was used. Pyrexia was abated to 37.2°C. 10 days after vaccination, the patient had pyrexia of 40.6°C. The patient took acetaminophen. He vomited on the same day. The patient died afterwards.	This is a case of which the patient had persisting pyrexia on the day of vaccination and from the 5 days after vaccination, which led to death at 10 days after vaccination. The causality with influenza vaccination cannot be assessed due to lack of information since detailed information regarding cause of pyrexia and the conditions that led to death were not obtained.
5	Male in 80s Name of adverse reaction: pneumonia and pyrexia Past history/complications: decubitus ulcer The patient had been bedridden for several years. He had been hospitalized for 2 months prior to influenza vaccination for the treatment of decubitus. The patient received influenza vaccination. Body temperature, pulse rate, and blood pressure before vaccination were 36.8°C, 72 bpm, and 110/82 mmHg, respectively. On the day of vaccination, the patient had 38°C level pyrexia from the evening. 1 day after vaccination, acute pneumonia was suspected as 39°C level pyrexia persisted. Meropenem trihydrate, fosfluconazole, and vancomycin hydrochloride were administered. Several days were passed without alleviation of pyrexia. On 6 days after vaccination, the patient fell into respiratory arrest and the death was confirmed.	Although pyrexia and pneumonia occurred immediately after vaccination, the causality with influenza vaccination cannot be assessed due to lack of detailed information such as laboratory findings etc.

WBC: White Blood Cell
CRP: C-Reactive Protein
CT: Computed Tomography Scan

Table 4. Sequelae case summary etc.

No.	Case summary	The result of a review by the committee
1	Female in 10s Name of adverse reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: None The patient received the first influenza vaccination. 9 days after the vaccination, she received the second vaccination. 24 days after the second vaccination, the patient complained of headache. In addition, the patient also complained of aggravation of numbness in the right hand, and made an outpatient visit to the emergency department. An analgesic was prescribed, and the patient was sent home. 28 days after the second vaccination, the patient noted general malaise. 29 days after the second vaccination, blurred vision developed. 30 days after the second vaccination, the patient became unable to recognize TV picture. 31 days after the second vaccination, the patient consulted an ophthalmologist. 32 days after the second vaccination, acute disseminated encephalomyelitis was suspected from the result of head MRI. The patient was hospitalized on the same day. Steroid pulse therapy was initiated on admission and 3 courses were conducted. Although the vision gradually recovered, visual acuity reduced. 38 days after the second vaccination, the patient was discharged. Thereafter, symptoms were controlled by the treatment with oral steroid.	Neurological symptoms have been observed since 24 days after the second vaccination and the patient was diagnosed as acute disseminated encephalomyelitis. The causality with influenza vaccination cannot be denied as there were no other factors to cause the neurological symptoms.
2	Male in 10s Name of adverse reaction: complex regional pain syndrome (reflex sympathetic dystrophy of the left hand) Past history/complications: none The patient received influenza vaccination. There were no marked changes immediately after vaccination. 30–60 minutes after vaccination, the patient noticed numbness and feeling cold of from left upper arm to maniphalanx, and visited hospital. At the time of consultation, consciousness lucid, muscular weakness of left forearm, and marked decrease in skin temperature were confirmed. Palpation of pulse at radius was good. Circulatory disorder peripheral was suspected. The patient was diagnosed as reflex sympathetic dystrophy of the left hand at another hospital and was hospitalized on the same day. Fluid replacement with steroid and vitamin preparation etc. as well as rest treatment were conducted. 3 days after vaccination, the patient was discharged. Weakness of left hand and feeling cold improved yet persisted at the time of discharge. Rehabilitation was conducted on outpatient visit afterwards. About 5 months after vaccination, the patient had been going to hospital as weakness persisted.	The causality between the event and the influenza vaccination cannot be ruled out based on the fact that the symptoms occurred on the vaccinated arm. However, other factors cannot be ruled out either since the symptoms occurred within 1 hour after the vaccination, which was relatively early, and the patient was an athlete and might have had muscle fatigue etc.

3	Female in 50s Name of adverse reaction: vasculitis cerebral Past history/complications: None The patient received influenza vaccination. About 2 weeks after vaccination, the patient had symptoms of common cold. The patient visited hospital as numbness in left side of face and upper extremities as well as slight fever, cough, nasal discharge, queasy, and throbbing headache manifested. 10 days after the hospital visit, although orientation was normal, memory impairment, constructional apraxia, lost sense of right/left, dyscalculia, and dressing apraxia developed. Blood test confirmed no abnormalities except for red blood cell sedimentation rate increased. Although cerebrospinal fluid examination indicated increased lymphocytes, various types of virus antibody/DNA tests indicated negative. 12 days after the hospital visit, numbness of left upper extremity/mouth angular. 13 days after vaccination, the patient was hospitalized. Diffusion-weighted image of MRI confirmed a high signal area in both sides of cortex of occipital lobe/subcortex. MRA and cerebral angiography confirmed sausage-like vascular stenosis/vasodilatation in both sides of anterior/middle/posterior cerebral artery. The patient was diagnosed as vasculitis cerebral based on the findings of cerebrospinal fluid examination and cerebral angiography. From 17 days after the hospital visit, steroid pulse therapy and cilostazol treatment were started. Although conditions and vasculitis cerebral were improved by virtue of these treatments, both sides of occipital lobes were left with irreversible damage. 43 days after the hospital visit, the patient was discharged from the hospital. She had sequelae of memory impairment.	Although the event occurred after vaccination, the possible influence of infection etc. acquired after vaccination is also considered. The causality with influenza vaccination cannot be assessed due to lack of relevant information such as the detailed information of vaccination and the post-vaccination course from the onset of the infection to onset of vasculitis cerebral.
4	Male under age of 10 Name of adverse reaction: facial palsy Past history/complications: psychomotor skills impaired, upper respiratory tract inflammation, and herpetic gingivostomatitis The patient received influenza vaccination. 4 days after vaccination, the patient had ptosis of left mouth angular and left eyelid closure difficulty. Facial palsy on the left side manifested. 5 days after vaccination, the patient visited hospital. He was diagnosed as facial palsy on the left side and bilateral otitis media. No abnormalities were confirmed in head CT. 6 days after vaccination, a wait-and-see approach was taken. 8 days after vaccination, antibacterial drug was prescribed for otitis media. 18 days after vaccination, there was a sign of recovery in facial palsy. The antibacterial drug was changed as eardrum redness persisted. 34 days after vaccination, although closure of left eyelid became possible, eardrum redness persisted. No abnormalities were found in CT of the temporal bone. Treatment for otitis media was completed.	Onset of the event occurred after vaccination. However, the causality with influenza vaccination cannot be assessed as the patient was infected with herpes virus prior to vaccination and other factors such as post-vaccinal otitis media cannot be ruled out.

	79 days after vaccination, marked laterality in the facial expression. 115 days after vaccination, swelling of left eyelid (oedema) manifested after varicella vaccination and laterality of palpebral fissures became obvious. 211 days after vaccination, asymmetry of face became particularly prominent when crying. Left eyelid ptosis was persisting.	
5	Male in 10s Name of adverse reaction: Guillain-Barre syndrome Past history/complications: none The patient received influenza vaccination. 6 days after vaccination, muscular weakness of dominant right side of the body. Sensory paralysis was noted. The patient presented Guillain-Barre syndrome. 7 days after vaccination, diplopia manifested. 9 days after vaccination, rate of peripheral nerve transmission in legs decreased. 12 days after vaccination, administration of gamma globulin was started. Improving tendency in the muscle strength was indicated and paralysis disappeared after a few hours. 16 days after vaccination, only headache persisted. Paralysis disappeared.	The causality with influenza vaccination cannot be denied as neurological symptoms had been observed since 6 days after vaccination and there were no other factors that caused neurological disorder.
6	Female in 50s Name of adverse reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: food allergy and calculus ureteric The patient received influenza vaccination. 17 days after vaccination, stabbing pain in the right side of anal region occurred. Around 20 days after vaccination, the patient experienced intermittent smarting pain from the waist to back of the thigh. The frequency increased steadily. 34 days after vaccination, the patient was hospitalized. 35 days after vaccination, the patient noticed weakness in both of the thighs. The weakness aggravated gradually. 37 days after vaccination, walking independently became impossible. Hypoaesthesia in lower legs manifested. 44 days after vaccination, the patient almost lost sensation precordium below. Although the pain from the waist to thigh disappeared around this time, weakness was worsened. The patient became almost unable to move legs on her own. 103 days after vaccination, the patient was being treated with steroid pulse and plasma exchange therapy.	Neurological symptoms have been observed since 17 days after vaccination. The patient was diagnosed as acute disseminated encephalomyelitis. The causality with influenza vaccination cannot be denied as there were no other factors to cause the neurological symptoms.

Table 5 Reports of adverse reactions by influenza vaccines in FY 2006 (reported regardless of causality)

	Total	Recovery	Death	Serious	Hospitaliza-tion	Sequelae	Others	N/A
Total	26	2	1	1	5	1	12	4
1 Immediate systemic reaction	2				1		1	
1A Anaphylaxis	2				1		1	
1B Systemic urticaria								
2 Encephalitis, encephalopathy								
3 Convulsion	2					1	1	
4 Movement disorder								
5 Other nerve disorders	1				1			
6 Local abnormal swelling (over elbows)								
7 Rash generalized	1							1
8 Pyrexia of 39°C and higher	4				1		3	
9 Other abnormal reactions	1	1						
10 Nonstandard reports	15	1	1	1	2		7	3
10A Local reaction (redness and swelling etc.)	6	1					4	1
10B Systemic reaction (pyrexia etc.)	3			1	2			
10C Others	6		1				3	2

(Note) Listed numbers are provisional figures and are subject to partial change in the future.

2

Revision of PRECAUTIONS (No. 190)

(1) Drugs

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated August 8 and 10, 2007.

<Acting mainly on gram-positive bacteria and mycoplasma>

1 Telithromycin

[Brand Name]

Ketek Tablets 300 mg (Sanofi-Aventis K.K.)

[Warning]

WARNING

Serious adverse reactions such as loss of consciousness and hepatitis may occur. This drug should be used only to treat infections for which other antibiotics cannot be used or are ineffective.

[Contraindications]

This drug is contraindicated in patients with myasthenia gravis (Worsening of conditions may occur. See "Adverse Reactions").

[Precautions of Dosage and Administration]

Loss of consciousness and visual disturbance may occur. Patients should be instructed to take this drug before bedtime generally.

[Adverse Reactions (clinically significant adverse reactions)]

Exacerbations of myasthenia gravis: Exacerbations of myasthenia gravis have been reported in patients. There have been reports of fatal acute respiratory failure in patients who take this drug for respiratory tract infections.

<Thyroid and parathyroid hormone preparations>

2 Dried Thyroid, Levothyroxine Sodium Hydrate

[Brand Name]

Thyradin Powder (Aska Pharmaceutical Co., Ltd.), etc.
Thyradin-S Powder, Thyradin-S Tablets 25, 50, and 100 (Aska Pharmaceutical Co., Ltd.), Levothyroxine Na Tablets 25 μg and 50 μg [SANDOZ] (Sandoz K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder with marked elevations of AST (GOT), ALT (GPT), and γ-GTP, pyrexia, and malaise, and jaundice may occur. Patients should be closely monitored, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.

<Hormones-Miscellaneous>

3 Cyclofenil

[Brand Name] Sexovid (Aska Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice:** Hepatic function disorder with elevations of AST (GOT), ALT (GPT), and γ-GTP, pyrexia, and malaise, and jaundice may occur. Patients should be closely monitored and if any abnormal findings are observed, administration of this product should be discontinued and appropriate measures should be taken.

<Urogenital and anal organ agents-Miscellaneous>

4 Silodosin

[Brand Name] Urief Cap. 2 mg and 4 mg (Kissei Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice:** Hepatic function disorder with elevations of AST (GOT), ALT (GPT) and jaundice may occur. Patients should be closely monitored, and appropriate measures, such as discontinuing administration, should be taken if any abnormal findings are observed.

<Habitual intoxication agents>

5 Disulfiram

[Brand Name] Nocbin (Mitsubishi Pharma Corporation)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice:** Hepatic function disorder with elevations of AST (GOT), ALT (GPT), γ-GTP, LDH, Al-P, and bilirubin and jaundice may occur. Patients should be closely monitored through periodic hepatic function tests. If any abnormal findings are observed, appropriate measures, such as discontinuing administration, should be taken.

<Antivirals>

6 Entecavir Hydrate

[Brand Name] Baraclude Tablets 0.5 mg (Bristol-Myers K.K.)

[Important Precautions] Administration of this drug to HIV/HBV co-infected patients who have hepatitis B virus and who are not receiving anti HIV therapy may cause emergence of drug-resistant HIV. Administration of this drug is not recommended in such patients.

<Vaccines>

7 Recombinant Absorbed Hepatitis B Vaccine (yeast derived)

[Brand Name] Bimmugen (The Chemo-Sero-Therapeutic Research Institute), Heptavax-II (Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Shock/anaphylactoid symptoms:** Shock/anaphylactoid symptoms (blood pressure decreased, dyspnoea, and pallor facial etc.) may occur. Patients should be closely monitored after vaccination. If any abnormalities are observed, appropriate measures should be taken.

<Mixed biological preparations>

8 Freeze-dried Live Attenuated Measles And Rubella Combined Vaccine

[Brand Name] Freeze-dried live attenuated measles and rubella combined vaccine "TAKEDA" (Takeda Pharmaceutical Company Limited), Mearubik (The Research Foundation for Microbial Diseases of Osaka University)

[Adverse Reactions] "The following information regarding adverse reactions is included in the package insert of freeze-dried live attenuated measles vaccine or freeze-dried live attenuated rubella vaccine." was omitted.

[Adverse Reactions (clinically significant adverse reactions)] **Encephalitis:** Encephalitis has been reported to occur. If any abnormalities are observed, appropriate measures should be taken.
Convulsion: Febrile convulsion may occur. If any abnormalities are observed, appropriate measures should be taken.

(2) Medical Devices

This section presents details of revisions to the PRECAUTIONS section of package inserts of medical devices that have been revised according to the Notification dated August 3, 2007.

1 Internal fluid pathway type needleless connectors

(A type in which the fluid pathway is established when a valve at the connecting site of this product is moved down by the press of the tip of the syringe injection port or the male luer of the drip infusion set etc. and establishing connection between the internal cannula and the drip infusion set etc. See Figures 1 and 2.)

[Precautions (interactions)]

(1) In connecting the drip infusion set, extension tubes, and syringe etc. (hereinafter referred to as "drip infusion set etc.") to this product, exchange for another product when the drug cannot be injected as pathway may not be established depending on the configuration of the tip of the injection port of a syringe or the male luer of the drip infusion set etc. Extra caution should be exercised in the case of conducting microinjection with a syringe pump etc.

(2) Prefilled syringes having the tip of the injection port with an internal diameter of ○ mm or less or extension tubes having the tip of the male luer with an internal diameter of △ mm and more should not be connected to this product. [Leakage of solution and infection may occur due to the breakage of this product or a tip of the injection port of a prefilled syringe when connecting a prefilled syringe having the tip of the injection port with an internal diameter ○ mm or less to this product. In addition, fluid pathway may not be established in the case of connecting extension tubes having the tip of the male luer with an internal diameter of △ mm and more to this product. Both evidences are certificated based on the company data.]

References

List of products of which connection to the internal fluid pathway type needleless connectors cannot be established due to the internal diameter of the tip of injection port of a prefilled syringe with an attached male luer lock.
(As of August 3, 2007)

Prefilled syringes with a male luer lock of which connection to the internal fluid pathway type needleless connectors is difficult			Internal fluid pathway type needleless connectors	
Name of the marketing authorisation holder	Name of the product	Internal diameter of the end (mm)	Bionector 2 and other models [unsuitable dimensions] 1.4 mm or less	CLAVE connector etc. [unsuitable dimensions] Less than 1.55 mm
Kirin Pharma Company, Limited	Gran Syringe 75	1.10	×	×
	Gran Syringe 150		×	×
	Gran Syringe M300		×	×
	Espo Injection 750 Syringe		×	×
	Espo Injection 1500 Syringe		×	×
	Espo Injection 3000 Syringe		×	×
Chugai Pharmaceutical Co., Ltd.	Epogin Injection Syringe 750	1.10	×	×
	Epogin Injection Syringe 1500		×	×
	Epogin Injection Syringe 3000		×	×
	Epogin Injection Syringe 6000		×	×

	Epogin Injection Syringe 9000		×	×
	Epogin Injection Syringe 12000		×	×
Bayer Yakuhin, Ltd.	Magnevist Syringe	1.1 (−0.1⁄+0.17)	×	×
Hikari Pharmaceutical Co., Ltd.	Ondansetron Injection 4 mg Syringe “HK”	1.50–1.69	○	×
	Dalteparin Na Syringe 5000 “HK”		○	×

2 Slit septum type needleless connector

(A type in which the fluid pathway is established when a slit septum is opened by the press of the tip of the syringe injection port or the male luer of the drip infusion set etc. See Figures 1 and 3.)

[Precautions (interactions)]

(1) In connecting the drip infusion set, extension tubes, and syringe etc. (hereinafter referred to as "drip infusion set etc.") to this product, exchange for another product when the drug cannot be injected as pathway may not be established depending on the configuration of the tip of the injection port of a syringe or the male luer of the drip infusion set etc. Extra caution should be exercised in the case of conducting microinjection with a syringe pump etc.

Figure 1. Usage example of needleless connector parts

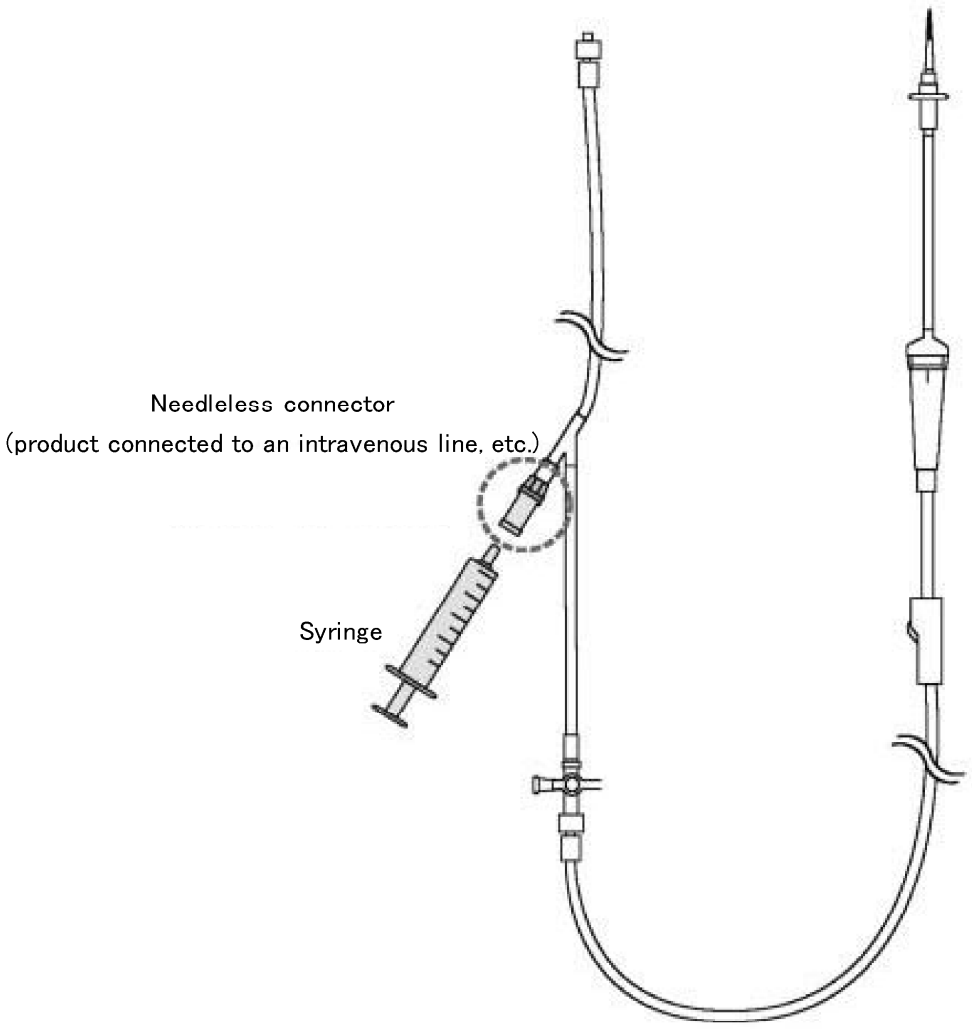
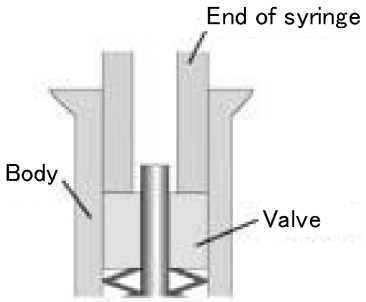
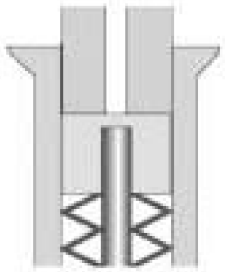


Figure 2. Internal fluid pathway type needleless connectors

(1) Appropriate connection

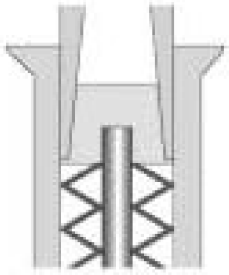


(2) Inappropriate connection 1



As shown in upper figure, leakage of solution and infection may occur due to the breakage of the injection port of syringe with an internal diameter of ○ mm or less

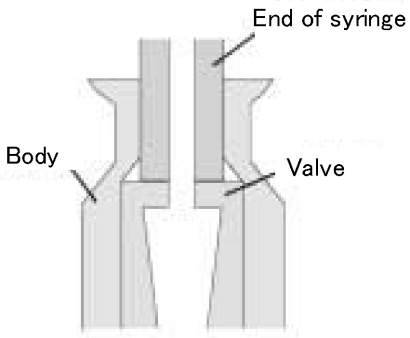
(3) Inappropriate connection 2



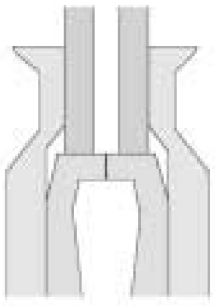
As shown in upper figure, pathway may not be established as valve cannot be opened in the case of connecting extension tubes with an internal diameter of △ mm or more

Figure 3. Slit septum type needless connector

(1) Appropriate connection



(2) Inappropriate connection



Pathway may not be established as valve cannot be opened depending on the configuration of the end of the syringe

3

List of products subject to Early Post-marketing Phase Vigilance

(As of September 1, 2007)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Follitropin Beta (Genetical recombination) Follistim Injection 50 and 75[*1]	Nippon Organon K.K.	March 16, 2007
Peginterferon Alfa-2a (Genetical recombination) Pegasys s.c. Injection 90 μg and 180 μg[*2]	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Ribavirin Copegus Tablets 200 mg	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Modafinil Modiodal Tablets 100 mg	Alfresa Pharma Corporation	March 28, 2007
Levonorgestrel-releasing Intrauterine Contraceptive System Mirena 52 mg	Bayer Yakuhin, Ltd.	April 16, 2007
Valaciclovir Hydrochloride Valtrex Granules 50%[*3]	GlaxoSmithKline K.K.	April 18, 2007
Entacapone Comtan Tablets 100 mg	Novartis Pharma K.K.	April 19, 2007
Pegvisomant (Genetical recombination) Somavert for s.c. Injection 10 mg, 15 mg, and 20 mg	Pfizer Japan Inc.	June 5, 2007
Salmeterol Xinafoate/Fluticasone Propionate Adoair 100 Diskus, 250 Diskus, and 500 Diskus	GlaxoSmithKline K.K.	June 8, 2007
Ciclesonide Alvesco 50 μg Inhaler 112 puffs, 100 μg Inhaler 112 puffs, and 200 μg Inhaler 56 puffs	Teijin Pharma Limited	June 8, 2007
Fondaparinux Sodium Arixtra Injection 1.5 mg and 2.5 mg	GlaxoSmithKline K.K.	June 8, 2007
Imidafenacin Uritos Tablets 0.1 mg	Kyorin Pharmaceutical Co., Ltd.	June 11, 2007
Imidafenacin Staybla Tablets 0.1 mg	Ono Pharmaceutical Co., Ltd.	June 11, 2007
Ezetimibe Zetia Tablets 10 mg	Schering-Plough K.K.	June 11, 2007
Bevacizumab (Genetical recombination) Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL	Chugai Pharmaceutical Co., Ltd.	June 11, 2007
Celecoxib Celecox Tablets 100 mg and 200 mg	Astellas Pharma Inc.	June 12, 2007
Sodium Risedronate Hydrate Actonel Tab. 17.5 mg	Ajinomoto Co., Inc.	June 15, 2007

Sodium Risedronate Hydrate Benet Tablets 17.5 mg	Takeda Pharmaceutical Company Limited	June 15, 2007
Monobasic Sodium Phosphate Monohydrate/Dibasic Sodium Phosphate Anhydrous Visiclear Tablets	Zeria Pharmaceutical Co., Ltd.	June 15, 2007
Amiodarone Hydrochloride Ancaron Injection 150	Sanofi-Aventis K.K.	June 22, 2007
Carteolol Hydrochloride Mikelan LA Ophthalmic Solution 1% and 2%	Otsuka Pharmaceutical Co., Ltd.	July 3, 2007
Darbepoetin Alfa (Genetical recombination) Nesp Injection Syringe 10 μg syringe, 15 μg syringe, 20 μg syringe, 30 μg syringe, 40 μg syringe, 60 μg syringe, and 120 μg syringe	Kirin Pharma Company, Limited	July 9, 2007
Fludarabine Phosphate Fludara Tab. 10 mg	Bayer Yakuhin, Ltd.	July 12, 2007
Estradiol l'estrogel 0.06%	Shiseido Co., Ltd.	August 9, 2007

*1: An additional indication for "the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamic-pituitary dysfunction"

*2: An additional indication for "the use in combination with ribavirin, for the improvement of viraemia in one of the following chronic hepatitis C: (1) serogroup 1 (genotype I (1a) or II (1b)) with high serum HCV-RNA loads, or (2) patients who failed interferon monotherapy or who developed reactivation (of chronic hepatitis C) following interferon monotherapy"

*3: An additional indication for "varicella"