Pharmaceuticals and Medical Devices Safety Information

No. 217 September 2005

Table of Contents

1. **Reports etc. on the adverse reactions of the influenza vaccines in FY2004** ····· 3

2. **Important Safety Information**

   1 Zedoary Powder and Japanese Tangle Powder Preparation ····· 8

3. **Revision of PRECAUTIONS (No. 169)**
   Paroxetine Hydrochloride Hydrate (and 9 others) ····· 11

4. **List of products subject to Early Post-marketing Phase Vigilance** ····· 15

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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Pharmaceuticals and Medical Devices Safety Information

No. 217 September 2005

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 the adverse reactions associated with influenza vaccines in FY2004**		This section presents the summarized reports of adverse reactions associated with the influenza vaccines in FY2004 and safety measures. The estimated number of shipments of the influenza vaccines in FY2004 was approximately 15.98 million vials. The number of adverse reactions reported by marketing authorisation holders and healthcare providers etc. in adverse reaction etc. reports in accordance with the Pharmaceutical Affairs Law amounted to 113 cases and 205 events. Among the most numerous adverse reactions reported, there were 22 cases of pyrexia, 17 cases of shock and anaphylactoid symptoms, 12 cases of hepatic function disorder etc., 11 cases of oedema, 11 cases of respiratory symptoms such as asthma, 10 cases of injection site redness and swelling etc., 8 cases of rash etc., 6 cases of Guillain-Barre syndrome, and 4 cases of ADEM.	3
2	**Zedoary Powder and Japanese Tangle Powder Preparation**	*P* *C*	Presents contents of revisions, reference materials and a summary of cases 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. 216).	8
3	**Paroxetine Hydrochloride Hydrate (and 9 others)**		Revision of PRECAUTIONS (No. 169)	11
4	**Products subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of September 1, 2005.	15

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

1

Reports etc. on the adverse reactions associated with influenza vaccines in FY 2004

(1) Introduction

Influenza is classified into Category II Diseases according to the amendment of the Preventive Vaccination Law in 2001.

Category II Diseases places emphasis on prevention for the individual. As immunization for these diseases is mainly conducted for personal preventive purposes, as opposed to being a duty or obligation, vaccinations are given only when an individual chooses to receive one.

According to the Preventive Vaccination Law, candidates for influenza vaccination are those who are aged 65 and older, and aged 60 and older and under aged of 65, who possess cardiac, renal, or respiratory dysfunction which severely limits one's daily life activities, and those who possess immune dysfunction due to human immunodeficiency virus (HIV) which makes it impossible to perform daily life activities. The efficacy of the current influenza HA vaccination is recognized internationally. Its efficacy in preventing the disease in the elderly and particularly in preventing aggravation of the disease has been confirmed in Japan.

Known adverse reactions of the influenza vaccination include injection site redness, swelling, and pain, as well as systemic symptoms of pyrexia, chill, headache, general malaise, and vomiting. Normally, symptoms disappear within 2 to 3 days after vaccination. As well, rash, urticaria, erythema, and pruritus are also known to occur immediately or within a few days after vaccination. Shock, acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome, convulsion, hepatic function disorder/jaundice, and asthmatic attack are reported as serious adverse reactions.

This section represents a summary of the reporting status and safety measures on adverse reactions associated with the influenza vaccines in FY 2004.

(2) Report on the adverse reactions of the influenza vaccination in FY 2004

Estimated amount of shipments of the influenza vaccines in FY 2004 was approximately 15.98 million vials. Marketing authorisation holders and healthcare providers etc. reported 113 cases and 205 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, the Pharmaceutical Affairs Law. Major reported adverse reactions consisted of 22 events of pyrexia, 17 events of shock and anaphylactoid symptoms, 12 events of hepatic function disorder etc., 11 events of oedema, 11 events of respiratory symptoms such as asthma, 10 events of injection site redness and swelling etc, 8 events of rash etc., 6 events of Guillain-Barre syndrome, and 4 events of ADEM.

Table 1 indicates the number of reported adverse reactions associated influenza vaccination by outcome and according to age. The results of a review of the influenza vaccination by a committee consisting of specialists in infectious disease and viruses (hereafter, "vaccine adverse reaction review committee") showed that, among cases of death and sequelae, there were no cases strongly suspected to have been affected by the influenza vaccination. As for the review results, **Tables 2 and 3** respectively show cases of death and sequelae.

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.

For reference, **Table 4** shows the number of events of reported adverse reactions associated with the influenza vaccination (including events of uncertain causality) in FY 2004 reported through this system. This is intended based on Immunization Practices for collecting the information of change in health conditions of the individuals in the form of periodic vaccinations in accordance with the Preventive Vaccination Law, and providing the public a broad range of information,.

Individuals targeted for reporting of adverse reactions from influenza vaccination according to the aforementioned system are those subject to routine vaccination, and differ from individuals targeted for reporting in reports on adverse reactions, etc. in accordance with the Pharmaceutical Affairs Law .

Table 1 Outcomes of adverse reactions cases associated with influenza vaccination in FY 2004 season (including cases for which a causality is unlikely)

Age Group	Total		Recovery/ remission		Unrecovered		Unknown		Sequelae		Death	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	113		92		10		5		2		4	
	46	66	36	56	2	7	2	3		2	2	2
Under age of 10	21		17		2		1		1			
	10	11	8	9	1	1	1			1		
10s	9		7		1		1					
	5	4	4	3		1	1					
20s	10		10									
	4	6	4	6								
30s	10		9		1							
	4	6	4	5		1						
40s	9		8		1							
	4	5	4	4		1						
50s	6		6									
	2	4	2	4								
60s	16		10		2		2		1		1	
	3	13	1	9	1	1		2		1	1	
70s	21		15		2		1				3	
	11	10	10	5		2		1			1	2
80s	8		8									
	3	5	3	5								
90s	2		2									
		2		2								
Unknown (age/sex unknown)	1				1							

Table 2 Cases of death associated with influenza vaccination in FY 2004 (including cases for which causality is unlikely)

No.	Case summary of adverse reactions	Evaluation by experts
1	Female in 70s Name of adverse reaction: pyrexia, sudden death At time of vaccination with influenza vaccine, her body temperature was 37.1°C. There was no pharynx ill sensation of. 4 days after vaccination, onset of 38°C pyrexia. There were no abnormal chest sounds,	From electrocardiogram findings, while death due to myocardial infarction was conjectured by the attending physician, the causality between this case of sudden death and vaccination cannot be assessed due to lack of information. As for the pyrexia, while 4 days had already passed since receiving the

	pharynx and pharynx ill sensation of. The patient was prescribed 2 g/day of isopropylantipyrine/allylisopropylacetylurea/acetaminophen/caffeine. 8 days after vaccination, the patient was found dead at home. Smoking history: 10 cigarettes/day. This was a case of sudden death of unknown cause, and as the attending physician observed ischaemic changes (ST depressed) on electrocardiogram, commented that sudden death due to myocardial infarction could be surmised.	vaccination, the causality with the vaccination cannot be denied.
2	Male in 70s Name of adverse reaction: cardio-respiratory arrest 35 minutes after influenza vaccination, the patient experienced chest discomfort, vomited bloody saliva. 45 minutes after vaccination, convulsion, rigidity, and cardio-respiratory arrest occurred. After artificial respiration started, defibrillation, epinephrine injection was used, and heartbeat regained. The patient developed multi-organ failure and died 15 days after vaccination. Attending physician commented that acute myocardial infarction or brain-stem vascular disorders could be the cause.	It is difficult to surmise that onset of myocardial infarction or cerebrovascular disorder could result from vaccination, and as basic diagnostic information (electrocardiogram, CT scan, etc.) were not obtained, it is difficult to assess causality. However, it is possible that acute myocardial infarction or brain-stem vascular disorders occurred after vaccination, and considering the time elapse, causality between the death and vaccination cannot be denied.
3	Male in 60s Name of adverse reaction: meningitis bacterial and pneumonia Although there was slight pyrexia, the patient received influenza vaccination. On the same night, the patient had 39°C pyrexia, and was prescribed loxoprofen sodium. The following day, there was increased peripheral blood leukocytosis, CRP 6.9 mg/dL (bacterial infection was suspected), and cefdinir and diclofenac sodium suppository were prescribed. Although fever resolved and the patient felt better 3 days after vaccination, he was prescribed salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate, loxoprofen sodium, cefdinir, and diclofenac sodium suppository. 5 days after vaccination, the patient experienced sudden confusional state accompanied by consciousness disturbed. The patient was diagnosed with meningitis bacterial and pneumonia due to pneumococcus by cerebrospinal fluid examination. The patient died 10 days after vaccination without improvement in state of consciousness. The attending physician noted that the patient was susceptible to infection due to diabetes mellitus, and the possibility cannot be denied that there was already an infection at time of vaccination and that the influenza vaccination indirectly aggravated the infection.	The cause of death was bacterial infection, and as it is difficult to surmise that the vaccination aggravated the bacterial infection, causality with the vaccination is unlikely.
4	Female in 70s Name of adverse reaction: hepatic failure After influenza vaccination, pyrexia, vomiting, queasy, and difficulty in eating developed. In the same month, there was onset of acute hepatic failure and the patient was hospitalized for 71 days after vaccination. Echogram showed hepatosplenomegaly, gallstones, cholecystitis, and	It is difficult to surmise that hepatic failure could occur from influenza vaccination. As there is no rationale for diagnosis or information on autopsy results, assessment cannot be made at this point in time.

	there was dramatic increase in pleural effusion and ascites. Although the treatment was performed, it had no effect and the patient died 4 months later. The attending physician commented that hepatic failure due to influenza vaccination cannot be denied.	

Table 3 Cases of sequelae associated with influenza vaccination in FY 2004 (including events for which a causality is unknown)

No.	Case summary of adverse reactions.	Evaluation by experts
1	Female under age of 10 Name of adverse reaction: dyskinesia, mental retardation The patient was administrated first vaccination 15 days before the second influenza vaccination. 7 days after the second vaccination, the patient had difficulty putting socks on. 9 days after vaccination, convulsion of the right upper leg was confirmed. 13 days after vaccination, chorea-athetosis of the right upper leg and consciousness disturbed developed. 27 days after vaccination, chorea-athetosis in the upper and lower extremities developed. The patient did not speak, high-amplitude slow-waves were observed, encephalitis and encephalopathy were diagnosed. Movement disorder and mental regression persisted. Blood test and cerebrospinal fluid examination did not detect viruses that could cause encephalitis and encephalopathy.	7 days after the second vaccination, neurological symptoms such as movements involuntary developed. Encephalopathy due to vaccination was suspected from later symptoms. Although information is lacking, considering elapse of time, causality with vaccination cannot be denied.
2	Female in 60s Name of adverse reaction: myelitis 3 days after influenza vaccination, chills, vomiting, and appetite impaired developed. 9 days after vaccination, myelitis developed. 33 days after vaccination, the patient was hospitalized and diagnosed with myelitis. The patient started administration of prednisolone 42 days after vaccination. Feeling strange prolonged. The attending physician commented that there was abdominal pain, rigidity, sensation of pressure, as well as slight increase in spinal fluid cell count and protein level.	As detailed clinical findings and clinical laboratory values could not be obtained, details are unknown and assessment is difficult.

Table 4 Reports of adverse reactions associated with influenza vaccines in FY 2004 (reported regardless of causality)

	Total	Recovery	Death	Serious	Hospitalization	Sequelae	Others	N/A
Total	41		4		8	2	13	14
1. Immediate systemic reaction	6				1		4	1
1A. Anaphylaxis	1						1	
1B. General urticaria	5				1		3	1
2. Encephalitis, encephalopathy	3		1		2			
3. Convulsion	1							1
4. Movement disorder	1						1	
5. Other nerve disorders	5					1	2	2
6. Local abnormal swelling (over elbows)	2							2
7. Rash generalized	4						2	2
8. Pyrexia of 39°C and higher	6		1		3		1	1

9. Other abnormal reactions	2		1		1			
10. Nonstandard reports	11		1		1	1	3	5
10A. Local reaction (redness and swelling etc.)								
10B. Systemic reaction (pyrexia etc.)	8		1			1	2	4
10C. Others	3				1		1	1

(3) Safety measures for influenza vaccination

Regarding acute renal failure/nephrotic syndrome and platelet count decreased cases for which it was agreed at last year's vaccine adverse reaction review committee that efforts to gather information would continue to be made, there were 2 cases of acute renal failure/nephritic syndrome (a total of 8 cases over the past 11 years) and 1 case of platelet count decreased (a total of 11 cases over the past 11 years) reported in FY 2004. Although including these adverse reactions in the clinically significant adverse reactions section was considered this year, it was determined that "there is insufficient basis for including them as adverse reactions in the clinically significant adverse reactions section" and was concluded to make continuous efforts would to gather information.

2

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. 216).

1 Powdered Zedoary, Powdered Kelp Containing Preparations

Brand Name (name of company)	Keimeigashinsan (powder), Keimeigashinsan S (powder), Keimeigashinsan S (fine granules)（Rohokeimeido Co.,Ltd）
Therapeutic Category	Over the counter drug
Indications	Anorexia (decreased appetite), feeling of bloating in stomach and the upper abdomen, indigestion, gasterasthenia, overeating (cynorexia), excessive drinking (overdrinking), heartburn, heavy stomach (slow digestion), knot in stomach, vomiturition (nauseous, upset stomach, hangover/feel sick from drinking, queasy, nausea), vomiting

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

[When not to use the product]

These products should not be used in the following persons.
People with a history of a hypersensitive reaction to this product (rash and redness, itching, oedema etc.).

[Consultation]

The following persons should consult with a doctor or pharmacist before using this product:
People with allergies or who have family members with allergies.
Persons with a history of an allergic reaction to a drug.
People who have been diagnosed with the following condition:
Hepatopathy
In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.
If the following symptoms are observed after taking this drug
Skin symptoms: rash and redness, itching, swelling
Gastrointestinal symptoms: abdominal pain, nausea and vomiting, diarrhoea
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.
Anaphylactoid symptoms: Immediately after administration, breathing difficulty, oedema, urticaria, rash etc. may occur.
Hepatic function disorder: General fatigue, jaundice (skin and white of the eyes become yellow) etc. may occur.

<Reference Information>

Company report
The number of reported relevant adverse reaction reports since April 2005 (since June 1992)
(exclusive of "causality is denied" and inclusive of "causality is unknown")
- Anaphylactoid symptoms: 3 cases (no fatal case) [13 cases (no fatal case)]
- Hepatic function disorder: 3 cases (no fatal case) [7 cases (no fatal case)]

The number of patients treated with Powdered Zedoary, Powdered Kelp Containing Preparations for a year estimated by MAH (Marketing Authorisation Holder): approximately 462000 (FY2004)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 30s	Upper abdominal pain (none)	1.5 g once	**Anaphylactoid symptoms** On day 1 of administration: The patient took 1/2 pouch (1.5 g) of this drug. Approx. 30 minutes after administration: Queasy, abdominal pain, and diarrhoea occurred. Later, there was onset of welts and dyspnoea accompanied by itching. Approx. 4 hours after administration: The patient was examined as out-patient, and treated with drip infusion of glycyrrhizin/glycine/cysteine, glutathione, an extract from inflammatory rabbit skin inoculated by vaccinia virus, hydroxyzine pamoate and oxygen inhalation. Welts resolved and were reduced to erythema, and symptoms were alleviated. The patient was hospitalized overnight as precaution. Drug administration was discontinued. 1 day after discontinuation: The patient was discharged as symptoms resolved. 28 days after discontinuation: Drug-induced lymphocyte stimulation test (prick test) was positive for this drug, powdered zedoary and turmeric powder.	Company report
	Concomitant medications: none				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 50s	Stomach discomfort (none)	9 g 15 days	**Hepatic function disorder** On day 1 of administration: Administration of 1 packet (3 g) of this drug 3 times/day was started to treat stomach discomfort. On day 5 of administration: The patient had malaise. On day 15 of administration (day of discontinuation): The patient had feelings of weakness and could not get up. 4 days after discontinuation: The patient was examined as out-patient, blood test showed high liver function values. The patient was diagnosed with hepatic function disorder and hospitalized. Immunologic test for liver disorder was negative. Therapy of rest and intravenous fluid replacement (glycyrrhizin/glycine/cysteine, glutathione etc.) was started. 11 days after discontinuation: Drug-induced lymphocyte stimulation test (DLST) was positive for this drug. 13 days after discontinuation: The symptoms were improved and the patient was discharged. 53 days after discontinuation: The patient was recovered through out-patient treatment.	Company report
	Concomitant medications: none				

Clinical Laboratory Values

	4 days after discontinuation	6 days after discontinuation	8 days after discontinuation	11 days after discontinuation	19 days after discontinuation	32 days after discontinuation	53 days after discontinuation
AST (GOT) (IU/L)	306	166	64	52	58	33	33
ALT (GPT) (IU/L)	769	583	342	180	128	59	54
Al-P (IU/L)	1850	1823	1709	1200	756	445	330
γ-GTP (IU/L)	508	444	376	259	154	73	41
Total bilirubin (mg/dL)	2.3	2.6	1.0	0.8	0.6	0.7	0.6
Total protein (g/dL)	7.8	--	--	7.3	7.9	--	7.8

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

3

Revision of PRECAUTIONS

(No. 169)

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. 216) (excluding those presented in "2. Important Safety Information" of this Bulletin), together with reference materials.

1 <Psychotropics> Paroxetine Hydrochloride Hydrate

[Brand Name]	Paxil Tablets 10 mg and 20 mg (GlaxoSmithKline K.K.)
[Contraindications]	Patients receiving pimozide
[Contraindications for concomitant use (do not use in combination)]	Pimozide
<Reference Information>	Company report

2 <Psychotropics> Pimozide

[Brand Name]	Orap Fine Granules, Orap Tablets 1 mg and 3 mg (Astellas Pharma Inc.)
[Contraindications]	Patients receiving a cytochrome P450 (CYP3A4) inhibiting agent (HIV protease inhibitor, azole antifungals, clarithromycin, erythromycin), paroxetine, or fluvoxamine.
[Contraindications for concomitant use (do not use in combination)]	Paroxetine, fluvoxamine
<Reference Information>	Company report

3 <Psychotropics> Fluvoxamine Maleate

[Brand Name]	Depromel Tablets 25 and 50 (Meiji Seika Kaisha, Ltd.), Luvox Tablets 25 and 50 (Solvay Seiyaku K.K.)
[Contraindications]	Patients receiving thioridazine, pimozide, and tizanidine hydrochloride
[Contraindications for concomitant use (do not use in combination)]	Thioridazine, pimozide
<Reference Information>	Company report

<Estrogen and progesterone preparations>

4 Norethisterone

[Brand Name] Norluten Tablets (5 mg) (Shionogi & Co., Ltd.), Primolut N (Nihon Schering K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Anaphylactoid symptoms:** Anaphylactoid symptoms may occur (dyspnoea, urticaria, angioedema, pruritus etc.), if these symptoms occur, discontinue administration and take appropriate measures.

<Reference Information> Company report

<Mixed hormone preparations, Contraceptives>

5 Norethisterone/Mestranol, Norethisterone/Ethinylestradiol

[Brand Name] Sophia-A, Sophia-C (Teikoku Hormone Medical Co., Ltd.), Norluten-D Tablets (Shionogi & Co., Ltd.), Ortho 777-21, Ortho M-21 (Janssen Pharmaceutical K.K.), Synphase T28 (Pfizer Japan Inc.), Norinyl T28 (Kaken Pharmaceutical Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Anaphylactoid symptoms:** Anaphylactoid symptoms may occur (dyspnoea, urticaria, angioedema, pruritus etc.). If these symptoms occur, discontinue administration and take appropriate measures.

<Reference Information> Company report

<Hemorrhoidal preparations>

6 Aluminum Potassium Sulfate/Tannic Acid

[Brand Name] Zione Injection/Lidocaine, Zione Injection (Mitsubishi Pharma Corporation)

[Important Precautions] Excessive blood pressure decreased and bradycardia may occur during or after administration. Ensure that emergency care can be provided immediately at any time and establish an IV line in advance.

[Adverse Reactions (clinically significant adverse reactions)] **Blood pressure decreased, bradycardia:** Excessive blood pressure decreased and bradycardia may occur during or after administration of this drug. Patients should be carefully monitored and if these symptoms occur, take appropriate measures.

<Reference Information> Company report

<Antidiabetic agents>

7 Pioglitazone Hydrochloride

[Brand Name] Actos Tablets 15 and 30 (Takeda Pharmaceutical Company Limited)

[Adverse Reactions (clinically significant adverse reactions)] Rhabdomyolysis characterized by myalgia, feelings of weakness, CK (CPK) increased, and myoglobin blood increased and urine myoglobin increased may occur. In such a case, administration should be discontinued, and appropriate measures should be taken.

<Reference Information> Company report

8 <Stimulation therapy agents> Bucillamine

[Brand Name] Rimatil Tablets 50 mg and 100 mg (Santen Pharmaceutical Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)]

Interstitial pneumonia, eosinophilic pneumonia, pulmonary fibrosis, pleurisy: Interstitial pneumonia, eosinophilic pneumonia, pulmonary fibrosis, and pleurisy (pleural effusion accumulation) may occur. If respiratory symptoms such as dyspnoea and cough and pyrexia etc. are observed, administration should be discontinued, and examinations such as chest X-ray should be immediately conducted, and take appropriate measures.

<Reference Information> Company report

9 <Synthetic narcotics> Fentanyl

[Brand Name] Durotep Patch 2.5 mg, 5 mg, 7.5 mg, and 10 mg (Janssen Pharmaceutical K.K.)

[Precautions of Dosage and Administration]

Initial patch dosage
In Japan, there are no cases of initial patch dosage exceeding 7.5 mg.
The conversion chart used to select initial patch dosage is based on a conversion ratio of an oral morphine dosage of 90 mg/day (45 mg/day for suppositories, 30 mg/day for injections) for 2.5 mg of this drug (fentanyl 0.6 mg/day).
A suitable initial patch dosage should be selected based on this conversion chart and caution should be exercised to avoid overdose.

[Important Precautions]

Patients etc. should be fully advised of major adverse reactions, specific method of use, precautionary points during administration, and storage method etc. before starting administration. In particular, patients should be instructed to immediately contact primary physician if symptoms of respiratory depression or consciousness disturbed etc. are observed.
If there is onset of pyrexia after application of this drug patch, as the temperature of this drug will elevate increasing the amount of fentanyl absorbed, caution should be exercised to avoid overdosing. Moreover, after application of this drug patch, make sure the patch site does not contact a heat source such as an electric pad, electric blanket, heated waterbed, infrared lamp, concentrated sun bath, sauna, or hot-water bottle etc.

[Adverse Reactions (clinically significant adverse reactions)]

Consciousness disturbed: Consciousness disturbed such as depressed level of consciousness and loss of consciousness etc. may occur. Patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
Shock, anaphylactoid symptoms: Shock and anaphylactoid symptoms may occur,. Patient's conditions should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.
Convulsion: Clonic or grand mal convulsions etc. may occur. If these symptoms occur, appropriate measures such as discontinuation of administration should be taken.

<Reference Information> Company report

10 Over the counter drugs
DEET

[Brand Name]	IIMEN Insect Repellent (Taisho Pharmaceutical Co., Ltd.), MUSIPALE ALPHA(Ikeda Mohando Ltd.) and others
[Precautions of Dosage and Administration]	Avoid indiscriminate application and only use this product when necessary such as outdoors where mosquitoes and gnats are prevalent. When applying this product on children (under age of 12), use the following standards for application as reference, under the supervision of a guardian etc. Do not apply this drug on the face. Do not use on infants under age of 6 months. Infants age of 6 months old and older and under aged 2: once a day Infants aged 2 and older and under aged of 12: 1-3 times/day Make sure not to get the drug in eyes, swallow, lick, or inhale the drug or rub eyes with application hand. In the case the drug gets in your eyes, immediately wash your eyes with large quantities of water or lukewarm water. Moreover, if you experience symptoms of illness etc., immediately visit and inform a physician that this drug contains ethanol and deet, and receive examination.

4

List of products subject to Early Post-marketing Phase Vigilance

(As of September 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Aluminum Potassium Sulfate/Tannic Acid / Zione Injection/Lidocaine, Zione Injection	Mitsubishi Pharma Corporation	March 15, 2005
Epinastine Hydrochloride / Alesion Dry Syrup 1%	Nippon Boehringer Ingelheim Co., Ltd.	March 23, 2005
Etanercept (Genetical recombination) / Enbrel 25 mg for s.c. Injection	Wyeth K.K.	March 30, 2005
Oxaliplatin / Elplat for Injection 100 mg	Yakult Honsha Co., Ltd.	April 6, 2005
Tacrolimus Hydrate / Prograf Capsules 0.5 mg and 1 mg*[1]	Astellas Pharma Inc.	April 11, 2005
Emtricitabine / Emtriva Capsules 200 mg	Japan Tobacco Inc.	April 19, 2005
Emtricitabine/Tenofovir Disoproxil Fumarate / Truvada Tablets	Japan Tobacco Inc.	April 19, 2005
Rosuvastatin Calcium / Crestor Tablets 2.5 mg and 5 mg	AstraZeneca K.K.	April 27, 2005
Bosentan Hydrate / Tracleer Tablets 62.5 mg	Actelion Pharmaceuticals Japan Ltd.	June 10, 2005
Tamibarotene / Amnolake Tablets 2 mg	Toko Pharmaceutical Industrial Co., Ltd.	June 13, 2005
Tocilizumab (Genetical recombination) / Actemra for Intravenous Infusion 200	Chugai Pharmaceutical Co., Ltd.	June 13, 2005
Adenosine / Adenoscan Injection 60 mg	Daiichi Suntory Pharma Co., Ltd.	June 21, 2005
Voriconazole / Vfend Tablets 50 mg and 200 mg, Vfend 200 mg for Intravenous Use	Pfizer Japan Inc.	June 27, 2005
Luliconazole / Lulicon Cream 1%, Lulicon Solution 1%	Pola Chemical Industries, Inc.	July 20, 2005
Fludeoxyglucose / FDGscan Injectable	Nihon Medi-Physics Co., Ltd.	August 1, 2005
Fludeoxyglucose / FDGscan-MP Injectable	The Medical and Pharmacological Research Center Foundation	August 1, 2005
Monteplase (Genetical recombination) / Cleactor Injection 400000, 800000, and 1600000	Eisai Co., Ltd.	August 5, 2005
Follitropin Beta (Genetical recombination) / Follistim Inj. 75 and 150	Nippon Organon K.K.	August 11, 2005

Note: Subject to additional indication etc.

*1: An additional indication for "Rheumatoid arthritis (only for cases which are not adequately responsive to conventional therapies"