Pharmaceuticals and Medical Devices Safety Information

No. 261 September 2009

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

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This translation of the original Japanese text is for information purpose only (in the event of inconsistency, the Japanese text shall prevail).

Pharmaceuticals and Medical Devices Safety Information

No. 261 September 2009

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 Reports

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

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

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

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, 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

Drug- associated serious skin disorders

1. Introduction

The occurrence of skin disorders as adverse drug reactions is well documented. Among serious skin disorders, Stevens- Johnson syndrome (oculomucocutaneous syndrome; SJS) and toxic epidermal necrolysis (TEN) are included.

The pathologies of SJS and TEN are described in Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 163 (November 2000), No. 177 (May 2002), No. 203 (July 2004), and No. 218 (October 2005). The adverse reactions reported to the MHLW between April 1, 1997 and September 30, 2005 are also summarized in these information.

Since the last information, adverse reaction reports have been collected for approximately 4 years. MHLW presents the summary of reported SJS and TEN up to July 31, 2009.

2. Stevens- Johnson syndrome (oculomucocutaneous syndrome) and toxic epidermal necrolysis

SJS is a condition which causes severe enanthema and skin erythema in the mucocutaneous junctions (lips, conjunctiva of the eyes, genital region, etc.), with pyrexia (38°C and more), often accompanied by necrotic epidermal disorders including blisters and epidermolysis. SJS is considered to be caused mainly by drugs. TEN is a condition which causes extensive erythema, marked necrotic epidermal disorders such as blisters, epidermolysis, and erosion of more than 10% of the entire body surface, with pyrexia (38°C and more) and enanthema. Among skin disorders, TEN is regarded as the most serious skin disorders caused by drugs.[1)] Although the occurrence frequency of SJS and TEN is extremely low such as 1–6 and 0.4–1.2 individuals per million/year, respectively, once they occur, they can be associated with a poor prognoses, and disorders of eyes, respiratory tract, etc. may remain even after skin symptoms have improved.[2),3)]

SJS and TEN can be caused by a wide range of drugs including antibiotics, antipyretics, analgesics, anti-inflammatory drugs, antiepileptics, gout preparations, sulfonamides, peptic ulcer drugs, hypnotic sedatives, anxiolytics, psychotropics, therapeutic drugs for glaucoma, muscle relaxants or hypertensive drugs. SJS and TEN have also been reported to occur by other drugs.[2, 4-7)]

See the Manuals for Management of Individual Serious Adverse Drug Reactions of "Stevens- Johnson Syndrome (Oculomucocutaneous Syndrome)"[8)] and "Toxic Epidermal Necrolysis."[9)] (Available at PMDA's website http://www.info.pmda.go.jp/) for detailed information on the initial symptoms, clinical course, treatment, etc. of SJS and TEN.

3. Adverse reactions reported to MHLW from October 1, 2005 to July 31, 2009

Drug-associated SJS and TEN reported up to September 30, 2005 were summed and presented in PMDSI No. 218. Therefore, MHLW summarizes adverse reactions reported from October 1, 2005 to July 31, 2009 in this review.

Among adverse reactions(including reports assessed by specialists as having no causality to drugs) reported by marketing authorization holders (MAHs) during the above period, there were 2,370 cases of SJS or TEN-associated adverse reactions reported (2.2% of the total 110,023 adverse reactions

reported for the period). Of these, 146 cases (6.2% of reported SJS or TEN-associated adverse reactions for the period) were reported to be possibly associated with over-the-counter drugs.

Regarding outcomes in the 2,370 events of SJS or TEN, 1,373 (57.9%) recovered or improved, 85 (3.6%) did not recover, 84 (3.5%) had sequelae, 239 (10.1%) died, and outcome was unknown in 589 (24.9%). When these figures collected over the past 4 years are compared with events collected over the approximately 2 year period from October 27, 2003 to September 30, 2005 that were presented in the PMDSI No. 218, the number of events in a year has increased by approximately 150, though with no remarkable difference has been observed in outcomes (**Table 1**). Since some events may be duplicated, and the events may be included that are thought to have no causality to drugs by specialists, it appears difficult to conclude that drug- associated SJS and TEN are on the rise based simply based on the recent trend of an increased number of events.

Reported drugs suspected to cause SJS or TEN amounted to 400 active ingredients. The most commonly reported drugs are shown in **Table 2** and **3** sorted by drug and therapeutic category, respectively. With regards to the order of events by their frequency, it must be noted that simple comparisons are not possible due to volume of drug sales, how to use, frequency of use, concomitant drugs, primary diseases, complications, etc. differing in each case.

4. Pathogenesis and mechanisms of Stevens- Johnson syndrome (oculomucocutaneous syndrome) and toxic epidermal necrolysis

Although the pathogeneses of SJS and TEN remain controversial, these disorders are thought to result from allergic skin reactions (type III allergy reactions) caused by infection from various viruses and microorganisms (herpes simplex virus, mycoplasma pneumoniae, bacteria, fungi, etc.), drugs, foods, endocrine abnormalities, malignant tumors, or physical stimuli. Drugs are considered a major cause with some literature estimating that 59% of SJS cases[4)] and more than 90% of TEN cases[4,5)] are caused by drugs.

Because the mechanisms of onset of these skin disorders have not been clarified yet, it is difficult to predict onset before administration of the drug. While as shown in **Table 4**, the presence of specific Human leukocyte antigens (HLAs) was reported in the majority of patients who developed these serious skin disorders after taking certain drugs such as carbamazepine and allopurinol when compared to the general population.[10-13)] These reports suggest that particular HLAs may be so-called genomic biomarkers that predict the onset of serious skin disorders associated with certain drugs. Given ethnic (or regional) differences in frequency of HLA alleles as well as the limited number of reports on the predictive performance of HLAs as genomic biomarkers (proportion of individuals with positive genomic biomarkers in the population experienced adverse reactions or, proportion of individuals with negative genomic biomarkers in the population experienced no adverse reactions), further studies are expected to address these issues.

Table 1 Number of adverse reactions reported as SJS and TEN and their outcomes (including reports reviewed by experts to have negative causality to drugs)

Period	Category	Number of adverse reactions reported as SJS or TEN (proportion of reported overall adverse reactions) events [mean/year]	Outcome of adverse reactions reported as SJS or TEN Number of events (proportion of SJS or TEN adverse reaction reports) events [mean/year]				
			Recovered or improved	Not recovered	Sequelae	Death	Outcome unknown, etc.
Oct. 1, 2005 to Jul. 31, 2009 (Approx. 3 years and 10 months)	All drugs (including OTC drugs)	2370 (2.2%) [618.3/year]	1373 (57.9%) [358.2/year]	85 (3.6%) [22.2/year]	84 (3.5%) [22.0/year]	239 (10.1%) [62.3/year]	589 (24.9%) [153.7/year]
	OTC drugs only	146	90 (61.6%)	5 (3.4%)	11 (7.5%)	3 (2.1%)	37 (25.3%)
Oct. 27, 2003 to Sept. 30, 2005* (Approx. 1 year and 11 months)	All drugs (including OTC drugs)	905 (1.7%) [472.2/year]	535 (59.1%) [279.1/year]	56 (6.2%) [29.2/year]	36 (4.0%) [18.8/year]	95 (10.5%) [49.6/year]	183 (20.2%) [95.5/year]
	OTC drugs only	61	40 (65.6%)	2 (3.3%)	3 (4.9%)	4 (6.6%)	12 (19.7%)

* See Pharmaceuticals and Medical Devices Safety Information No. 218

Table 2 Most frequently reported suspected drugs (by drug)

Drug name	Number of reported events
Allopurinol	161
Carbamazepine	131
Loxoprofen sodium hydrate	93
Acetaminophen	68
Diclofenac sodium	54
Zonisamide	49
Salicynamide/acetaminophen/ anhydrous caffeine/promethazine methylenedisalicylate	45
Clarithromycin	42
Phenobarbital	39
Levofloxacin hydrate	39

Table 3 Most frequently reported suspected drugs (by therapeutic category)

	Therapeutic category	Number of reported events
All drugs (including OTC drugs)	Antibiotics	397
	Antipyretics and analgesics, anti-inflammatory agents	364
	Antiepileptics	267
	Gout preparations	166
	Combination cold remedy	139
	Peptic ulcer agents	132
	Synthetic antibacterials	96
OTC drugs only	Combination cold remedy	84
	Antipyretics and analgesics, anti-inflammatory agents	47
	Nutrients, tonics-miscellaneous	4
	Otological agents	2
	Kampo medicines	2

Table 4 Frequency of HLA alleles in patients developing SJS or TEN after drug administration

Drug name	HLA allele	Ethnic origin (Region)	Proportion of HLA positive in individuals with SJS or TEN	Proportion of HLA positive in general population	Odds ratio (95% CI)	Reference No.
Carbamazepine	*HLA-B*1502*	Han Chinese (Taiwan)	59/60	6/144*	1357 (193-8838)	10
		Asians living in western countries	4/4	—	—	11
		Caucasians	0/8	—	—	11
		Japanese	0/7	0/486	—	12
Allopurinol	*HLA-B*5801*	Han Chinese (Taiwan)	51/51	19/93	394 (23-6665)	13
		Caucasians	15/27	28/1822	80 (34-187)	11
		Japanese	4/20	6/986	41 (11-159)	12

* Carbamazepine-treated individuals who did not develop SJS or TEN

5. Conclusion

Occurrence of SJS or TEN is rare but once they occur, they may lead to fatal outcomes resulting from complications such as multi-organ failure. They are serious skin disorders where disorders of the eyes, respiratory tract or other areas may remain even after skin conditions improve. These skin disorders, although rare, may occur irrespective of the drug administered.

When rash and accompanying hyperthermia develops after drug administration and SJS or TEN is suspected, the suspected drug should be discontinued and the patient should be promptly referred to a dermatologist. When healthcare providers administer or sell drugs commonly reported for such adverse reactions including antibiotics, antipyretics, analgesics, anti-inflammatory agents, antiepileptics, gout preparations, combination cold remedy, antiulcer agents and synthetic antibacterials, they should inform patients of the initial symptoms of these adverse reactions, and advise them to seek immediate medical attention if such symptoms develop.

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2

SSRIs/SNRIs and harmful behavior to others

1. Background

On May 8, 2009, the Drug Safety Committee on MHLW Drug Safety Pharmaceutical Affairs and Food Sanitation Council carefully reviewed domestic adverse reactions reports related to selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors (SNRIs), such as hostility, aggression, and relevant harmful behavior to others. The committee adopted a need to include additional cautionary statements regarding excitement, aggression, and excitability as well as patients' background indicating potential for behavior harmful to other in the PRECAUTIONS section in package inserts of related drugs. MHLW required MAHs to revise PRECAUTIONS in package inserts on the same day.[1,2)] (See PMDSI No. 258 [June 2009].)

Of collected spontaneous reports by pharmaceutical companies to PMDA, PMDA conducted the case series of SSRIs/SNRIs-related adverse reactions reports such as harmful behavior to others previously reviewed by the Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council as above. In order to describe risk factors for harmful behavior to others exploratory. The findings of the review are summarized in the following.

There are a few researches about harmful behavior to others in SSRIs/SNRIs-treated patients, the main subject of this review. On the contrary, suicide-related behavior has been documented in numerous epidemiological researches, including case control studies based on large databases, in which various background factor-related risks were quantified. Furthermore, when the U.S. regulatory authorities took action to address risks of suicidal ideation and suicide attempt in young patients treated with SSRIs/SNRIs in March, 2004, they stated that the treatment regimen needs to be altered when symptoms such as harmful behavior to others develop.[3,4)] In view of these above, known risk factors for suicide-related behavior have been reviewed mainly to identify risk factors for harmful behavior to others.

2. Method

■Drugs

Paroxetine hydrochloride hydrate, fluvoxamine maleate, sertraline hydrochloride, and milnacipran hydrochloride

■Adverse reactions

Medical conditions categorized as Standardized MedDRA Query (SMQ) "hostility/aggression," medical conditions that correspond to symptoms related to harmful behavior to others described in the FDA Talk Paper, or other medical conditions considered by companies as adverse reactions related to harmful behavior to others

■ Reports

Domestic adverse reaction reports provided by MAHs in accordance with the Pharmaceutical Affairs Law Article 77, 4-2. Reports on adverse reactions observed in infants of women treated with SSRIs or SNRIs during pregnancy were excluded (two reports of irritability, both of which were associated with paroxetine hydrochloride hydrate). Among target adverse reactions, non-serious adverse reactions were also excluded.

■Analysis

We conducted overall tabulation by patient background and tabulation by level of harmful behavior to others* and calculated the proportions.

* Levels of harmful behavior to others were defined as follows for use in tabulation based on information of the clinical course of each case.

Level 2: Presence of harmful behavior to others
Case of injury such as homicide. For instance, a case that describes a clinical course that includes stabbing with a knife or violent behavior to family or other patients

Level 1: Presence of harmful behavior to others
Case of injury such as homicidal ideation. For instance, a case that describes a clinical course that includes verbal abuse or tendency to lose one's temper

Level 0: Absence of harmful behavior to others
A case in which no specific information on harmful behavior to others is described, but where the reported adverse reaction corresponds to any of the target adverse reactions.

3. Summary of results

- Number of cases analyzed: 222 cases

- Sex: 111 women, 110 men (unknown: 1). As for Level 0, proportion of women was higher than that of men, while as for Level 2, proportion of men was higher than that of women.

	Level of harmful behavior to others						
	0		1		2		
	Number of cases	%	Number of cases	%	Number of cases	%	Total
Total	130	59%	61	28%	30	14%	221
Sex							
Women	79	71%	25	23%	7	6%	111
Men	51	46%	36	33%	23	21%	110

(Line %)

* Sex unknown: 1 case

- Age: median 41 (first quantile 28, third quantile 59), minimum 12, maximum 91. The higher the level of harmful behavior to others, the lower the median age.

	Level of harmful behavior to others			All levels
	0	1	2	
Number of cases	126	58	27	211
Age				
Minimum	12	14	13	12
25% point	28	30	28	28
Median	45	40	31	41
75% point	59	57	53	59
Maximum	91	85	70	91

* Age unknown: 11 cases

- Main disease name: The most common disorder was "major depression or depression" (74 cases), followed by "depressed state" (36 cases). Regarding patients diagnosed with "major depression or depression", there was a higher proportion of Level 0, and a lower proportion of Level 2 patients compared to those with other disorders. Meanwhile, regarding patients with "depressed state", "anxiety disorder", "obsessive-compulsive disorder" or "bipolar disorder", the proportion of Level 0 was relatively low. Regarding patients with "depressed state", "anxiety disorder" or "obsessive-compulsive disorder", in particular, the proportion of Level 2 was relatively high.

	Level of harmful behavior to others						
	0		1		2		
	Number of cases	%	Number of cases	%	Number of cases	%	Total
Total	130	59%	61	27%	31	14%	222
Main disease name*							
Major depression	27	73%	7	19%	3	8%	37
Depression other than major depression	6	67%	2	22%	1	11%	9
Depression that is unknown to be major depression or not	21	75%	7	25%	0	0%	28
Depressed state	19	53%	9	25%	8	22%	36
Anxiety disorder	6	43%	5	36%	3	21%	14
Panic disorder	9	69%	2	15%	2	15%	13
Post-traumatic stress disorder	1	25%	3	75%	0	0%	4
Obsessive-compulsive disorder	4	36%	5	45%	2	18%	11
Developmental disorder	1	50%	0	0%	1	50%	2
Alcoholism (abuse)	1	100%	0	0%	0	0%	1
Bipolar disorder	14	54%	9	35%	3	12%	26
Other	15	54%	6	21%	7	25%	28
Unknown	23	51%	16	36%	6	13%	45

(Line %)

* Multiple answers allowed (total number of answers)

- Comorbidity: Comorbidity was "present" in 110 cases, "absent" in 47 cases, and "unknown" in 65 reports. The most frequent comorbidity was personality disorder (13 events) (data not shown). By the level of harmful behavior to others, the proportion of Level 2 was higher in patients with "present" compared to patients with "absent".

	Level of harmful behavior to others						
	0		1		2		
	Number of cases	%	Number of cases	%	Number of cases	%	Total
Total	130	59%	61	27%	31	14%	222
Comorbidity							
Present	63	57%	29	26%	18	16%	110
Absent	32	68%	11	23%	4	9%	47
Unknown	35	54%	21	32%	9	14%	65

(Line %)

4. Discussion

- Types of drugs:This survey is based on the spontaneous reports; therefore, drug type-specific analysis was not performed due to any reporting bias.
- Sex: Regarding SSRI-related adverse reactions in the type of suicide, it is considered that women have a higher risk of suicidal ideation or suicide attempt compared to men, while men have a higher risk of suicidal behavior compared to women.[5)] This review found that the proportion of Level 0 in women was high, suggesting that women are less likely to go beyond an attempt or ideation of harmful behavior to others, while the proportion of Level 1 or 2 in men was high, suggesting that men are more likely to actually devlop harmful behaviors to others.
- Age: Younger generation is an already known risk factor for SSRI-related adverse reactions of suicide-related behavior, with a cautionary statement included in package inserts stating that individuals aged 24 and younger have a higher risk of suicidal ideation or suicide attempt.[6)] This survey has found as well that younger ages are apt to show higher levels of harmful behavior to

others.

- Main disease name and comorbidity: Patients with "depressed state", "anxiety disorder", or "obsessive-compulsive disorder" were more likely to exhibit higher levels of harmful behavior to others when compared to those with "major depression or depression. Patients with comorbidity were associated with higher levels of harmful behavior to others.
- History of impulsive behavior: Past history is a known risk factor for SSRI-related adverse reactions in the form of suicide.[7,8] This review revealed that patients with a history of impulsive behavior were likely to exhibit higher levels of harmful behavior to others.
- In this review, it's difficult to evaluate this issue due to lack of available information regarding details of prescription (such as medication period, concomitant medications).

This survey is the case series based on the spontaneous reports without control group. Though limitations such as missing data and underreporting existed, several potential risk factors have been identified with explorative analyses. In addition, within this analysis, it has been confirmed that the profile of potential risk factors may be similar to those for suicide-related behavior. In order to further confirm the result of the review, the risks should be quantified by more appropriate researches such as observational, studies with control group that focus on risk factors.

Major potential risk factors identified in this review have been already described in package inserts of the relevant drugs. In case of use of SSRIs/SNRIs, health care providers should stay alert for any changes in the condition of patients during the clinical course of treatment.

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3

Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated August 7, 2009.

1 Varenicline tartrate

Brand name (name of company)	Champix Tablets 0.5 mg and 1 mg (Pfizer Japan Inc.)
Therapeutic Category	Non-main therapeutic purpose agents - Miscellaneous
Indications	Aid to smoking cessation in nicotine-dependent smokers

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

[Warning]

WARNING

Smoking cessation with or without treatment is reported to be associated with a variety of symptoms and may exacerbate pre-existing psychiatric illnesses. Although causality to this drug is unknown, depressed mood, anxiety, feeling irritated, excitement, change in behavior or idea, mental disorder, mood variable, aggressive behavior, hostility, suicide ideation, and suicide have been reported. Patients treated with this drug should be carefully monitored accordingly.

[Careful Administration]

Patients with a history of psychiatric disorders including schizophrenia, bipolar disorder, depression etc.

[Important Precautions]

Smoking cessation with or without treatment has been reported to be associated with various symptoms (discomfort, depressed mood, insomnia, bad mood, frustration, anger, anxiety, concentration difficulty, restlessness, heart rate decreased, increased appetite, weight increased, etc.). These symptoms may worsen underlying mental conditions. It has also been reported that depressed mood, anxiety, irritation, excitement, changes in behavior or idea, mental disorder, mood variable, aggressive behavior, hostility, suicidal ideation, and suicide occurred in patients who had attempted to quit smoking with this drug, although the causality to this drug is unknown. Patients administered with this drug should be carefully monitored. In addition, these symptoms also may occur after discontinuation of this drug. Patients should also be instructed to stop taking this drug and contact a physician etc. immediately if such symptoms and/or behaviour occur.

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens- Johnson syndrome), erythema polymorphe: Oculomucocutaneous syndrome (Stevens- Johnson syndrome),and erythema polymorphe etc. may occur. If symptoms including rash occur, discontinue this drug and appropriate measures should be taken.

Angioedema: Angioedema with symptoms of swelling in face, tongue, lip, and throat etc. may occur. If these symptoms occur, discontinue this drug and

appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases(for which causality to the drug could not be denied) around the last 1 year (May 8, 2008 to July 10, 2009)
• Psychoneurotic symptoms: 22 cases (no fatal cases)
The number of patients treated with Varenicline tartrate for a year estimated by MAH: approximately 189,000 patients (July 2008 to June 2009)
Marketed in Japan in: May 2008

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Smoking cessation therapy (Diabetes, hyperlipidemia, hyperuricemia)	0.5 mg for 3 days ↓ 1 mg for 4 days ↓ 2 mg for 16 days ↓ 1 mg for 15 days	**Somnambulism, consciousness clouding, judgment impaired** On day 1 of administration: The patient had a history of smoking 20 cigarettes a day for 35 years. This drug was administered at 0.5 mg. On day 4 of administration: The dose was increased to 1 mg. On day 8 of administration: The dose was increased to 2 mg. On day 9 of administration: The patient experienced nausea and abdominal distension. On day 14 of administration: The patient experienced excessive dreams, dysthymia, absent-mindedness. Mosapride citrate hydrate was initiated. The patient felt that he didn't care if he was to jump from a building (not suicidal thoughts) and felt like he was sleepwalking, foggy, and unvigilant, though he did not mention the symptoms at the time of the visit. On day 24 of administration: The patient complained about severe nausea. He looked blank and was slow in response. He was instructed to reduce the dose to 1 mg. On day 29 of administration: The patient reported the past clinical course, at which point the physician first became aware that the patient had had feelings about jumping (sleepwalking, foggy, and unvigilant feelings). On day 39 of administration (day of discontinuation): The drug was discontinued after nausea and palpitation persisted. 2 days after discontinuation: Disappearance of sleepwalking, foggy, and unvigilant feelings was confirmed. Absent-mindedness, nausea, and abdominal detention ameliorated 2–3 days after drug discontinuation.
	Concomitant medications: voglibose, pravastatin sodium, allopurinol, mosapride citrate hydrate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Nicotine dependence (Myocardial ischemia, insomnia, chronic pancreatitis, myocardial infarction)	0.5 mg for 3 days ↓ 1 mg for 4 days ↓ 2 mg for 56 days	**Depression, abnormal behavior** 7 days before administration: The patient had a history of smoking 20 cigarettes a day for 38 years. Treatment of nicotine dependence was initiated. On day 1 of administration: The drug was initiated at 0.5 mg. CO concentration was 31 ppm. On day 4 of administration: The dose was increased to 1 mg. On day 8 of administration: The dose was increased to 2 mg. The patient quit smoking (he smoked 10 or fewer cigarettes a day from day 1 until day 8). On day 9 of administration: The patient felt that the back of his hand smelled like tobacco smoke. On day 16 of administration:

				No abnormal dreams or anorexia. On day 21 of administration: The patient smoked two cigarettes and they tasted bad. On day 30 of administration: CO concentration was 1 ppm. On day 31 of administration: The patient said that he had smoked two cigarettes and they tasted bad. On day 44 of administration: The patient said that he ate snacks more often. CO concentration was 1 ppm. On day 57 of administration: The patient said that he ate snacks more often. No abnormal dreams. CO concentration was 1 ppm. On day 61 of administration: The patient felt that his odor (tobacco odor) was strong enough to fill the room he was in and he became anxious. Out of an intense feeling of loneliness he made a phone call to his acquaintance, his talking was nonsensical. On day 64 of administration (day of discontinuation): The patient felt ill and went home after lunch. He quit the medication on his own judgment. 2 days after discontinuation: After drug discontinuation the patient experienced persisting insomnia and was unable to sleep well. 3 days after discontinuation: In the morning when the patient used the rest room he felt that he saw a small creature (praying mantis or grasshopper) in the lavatory basin. He consulted a nurse and visited a psychiatrist in the morning. Oral perphenazine maleate was prescribed and he took a single dose. He later took a nap for 2 hours at a desk. After awakening he felt restless and rode a bicycle for 80 minutes (he had a habit of riding a bicycle for about 20 minutes). He bought a pack of cigarettes and smoked five cigarettes during the ride. In the evening he became delirious while talking with an acquaintance and started to behave violently. He was immediately transferred to a hospital, though he has no recollection of this. 4 days after discontinuation: The patient came to his senses and realized that he was staying in a hospital. He then slept until the morning. He had a checkup in the morning and was discharged from the hospital. On later consultation with a psychiatrist the medication was changed from perphenazine maleate to nitrazepam 5 mg and mianserin hydrochloride 10 mg. 7 days after discontinuation: The patient visited the hospital where his drug was prescribed, and smoking cessation therapy with this drug was discontinued. The abnormal behavior, visual hallucinations and tobacco odor had disappeared (date unknown).
	Concomitant medications: aspirin, zolpidem tartrate, oxatomide			

4

Revision of PRECAUTIONS

(No. 209)

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 7, 2009 (excluding those presented in "3. Important Safety Information" of this Bulletin).

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1 <Antiarrhythmic agents>
Cibenzoline succinate (oral dosage form)

[Brand Name] Cibenol Tablets 50 mg and 100 mg (Astellas Pharma Inc.), and others

[Important Precautions] Patients being treated with this drug should be frequently monitored with periodic examinations of ECG, pulse rate, blood pressure, and cardiothoracic index. When abnormalities including prolonged PQ intervals, increased QRS duration, prolonged QT, bradycardia, or decreased blood pressure are observed, the dose should immediately be reduced or administration discontinued.
Cardiac arrest may occur especially in the following patients or situations. In such cases, extreme caution should be exercised when administrating**,** including dosage such as initiating administration with a low dose and carrying out frequent assessments of the patient's ECG.
1) Patients with underlying heart disorders (myocardial infarction, valvulopathy, cardiomyopathy, etc.) at risk of heart failure
2) Elderly patients
3) Concomitant use with other antiarrhythmic drugs
4) Patients with impaired kidney function

[Adverse Reactions (clinically significant adverse reactions)] **Arrhythmogenic effect:** Ventricular fibrillation, ventricular tachycardia (including torsades de pointes), or arrhythmia supraventricular may occur, leading to cardiac arrest. ECG examinations should be performed periodically and if any abnormal changes are observed administration of the drug should be discontinued and appropriate measures taken, such as administration of antiarrhythmic drugs.

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2 <Antiarrhythmic agents>
Cibenzoline succinate (injectable dosage form)

[Brand Name] Cibenol Injection (Astellas Pharma Inc.)

[Important Precautions] Patients being treated with this drug should be continuously monitored for blood pressure and ECG. Cardiac arrest may occur in the following patients or situations. In such cases, extreme caution should be exercised when administrating, including dosage such as initiating administration with a low dose and close monitoring of the patient. If abnormalities including prolonged QRS or QT, bradycardia, and excessively decreased blood pressure are observed, administration should be discontinued immediately.
1) Patients with underlying heart disorders (myocardial infarction, valvulopathy, cardiomyopathy, etc.) at risk of heart failure
2) Elderly patients or patients with impaired kidney function
3) Concomitant use with other antiarrhythmic drugs

[Adverse Reactions (clinically significant adverse reactions)]	**Arrhythmogenic effect:** Ventricular fibrillation, ventricular tachycardia (including torsades de pointes), or arrhythmia supraventricular may occur and lead to cardiac arrest. If any abnormal changes in a patient's ECG is observed administration of the drug should be discontinued and appropriate measures taken such as administration of antiarrhythmic drugs.

<Genital organ agents>

3 Estriol(Preparations for Vaginal Application)

[Brand Name]	ESTRIEL VAGINAL Tab. 0.5mg (MOCHIDA Pharmaceutica CO., LTD.), HOLIN-V VAGINAL TABLETS 1mg (ASKA Pharmaceutical CO.,LTD.) and others
[Contraindications]	Patients with a history of hypersensitivity to any components of this drug
[Adverse Reactions (clinically significant adverse reactions)]	**Shock, anaphylactoid symptoms:** Shock or anaphylactoid symptoms may occur. Patients should be carefully monitored and if abnormalities such as rash, flushing, dyspnoea, or decreased blood pressure are observed, administration of this drug should be discontinued and appropriate measures should be taken.

<Blood and body fluid agents- Miscellaneous>

4 Cilostazol

[Brand Name]	Pletaal powder 20%, Pletaal tablets 50mg and 100mg (Otsuka Pharmaceutical Co., Ltd) and others
[Careful Administration]	Patients with renal disorders
[Adverse Reactions (clinically significant adverse reactions)]	**Acute renal failure:** Acute renal failure may occur. Patients should be carefully monitored through renal function analyses and if such abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Miscellaneous metabolism agents >

5 Mycophenolate mofetil

[Brand Name]	CELLCEPT 250 (Chugai Pharmaceutical Co., Ltd)
[Adverse Reactions (clinically significant adverse reactions)]	**Pancytopenia, neutropenia (below 500/μL), agranulocytosis, leukopenia, thrombocytopenia, anaemia, aplasia pure red cell:** Since such symptoms may occur, conditions of the patient should be carefully monitored through periodic blood test. If any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be taken.

< Antineoplastics-Miscellaneous >

6 Imatinib Mesilate

[Brand Name] Glivec Tablets 100mg (Novartis Pharma K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Rhabdomyolysis:** Rhabdomyolysis such as myalgia, feelings of weakness, CK (CPK) increased, myoglobin blood increased or myoglobin urine increased may occur. If such symptoms are observed, administration should be discontinued and appropriate measures should be taken.

<Synthetic antibacterials >

7 Garenoxacin Mesilate Hydrate

[Brand Name] Geninax Tablets 200mg (Toyama Chemical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Psychiatric symptoms such as hallucination, delirium:** Since hallucination or delirium may occur, patients should be carefully monitored. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

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

< Over the counter drugs >

8 External preparations containing testosterone
External preparations containing methyltestosterone

[Brand Name]

<External preparations containing testosterone>
Glowmin, Tonos, Hairgrown (Daito Pharmaceutical Co., Ltd.), Onoc (Kikuriu Seiyaku), Dantelmon M Paster (Harasawa Pharmaceutical Co., Ltd.)

<External preparations containing methyltestosterone>
OTTOPIN-S, OTTOPIN external hormone spread (VITALIS Pharmaceutical Co., Ltd.), MICROGEN PASTAE (Keihodo Pharmaceutical Co., Ltd.)

[When not to use the product]

Drug should not be administered to anyone other than the intended recipient.

(1) Wash hands thoroughly after use with soap and lukewarm water.
(2) Be careful not to contact with anyone other than the intended recipient. If the drug accidentally comes into contact with someone other than the intended recipient it should be washed off immediately.
(3) When there is possibility that the site of drug application will come into contact with another person, the site should be washed thoroughly with soap and lukewarm water.

5

List of products subject to Early Post-marketing Phase Vigilance

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

(As of September 1, 2009)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Dasatinib Hydrate SPRYCEL Tablets 20 mg and 50 mg	Bristol Myers K.K.	February 2, 2009
Nilotinib Hydrochloride Hydrate TASIGNA Capsules 200 mg	Novartis Pharma K.K.	February 16, 2009
Lanthanum Carbonate Hydrate Fosrenol Chewable Tablets 250mg and 500mg	Bayer Yakuhin, Ltd.	March 11, 2009
Omalizumab（Genetical Recombination） Xolair for s.c. injection	Novartis Pharma K.K.	March 13, 2009
Candesartan Cilexetil / Hydrochlorothiazide ECARD Combination Tablets LD, ECARD Combination Tablets HD	Takeda Pharmaceutical Company Limited	March 13, 2009
Zonisamide TRERIEF Tablets 25mg	Dainippon Sumitomo Pharma Co., Ltd.	March 13, 2009
Valsartan/Hydrochlorothiazide Co-DIO Combination Tablets MD, Co-DIO Combination Tablets EX	Novartis Pharma K.K.	March 13, 2009
Ranibizumab（Genetical Recombination） LUCENTIS solution for intravitreal injection 2.3mg/0.23mL	Novartis Pharma K.K.	March 13, 2009
Nalfurafine Hydrochloride REMITCH CAPSULES 2.5μg	Toray Industries, Inc.	March 24, 2009
Azithromycin Hydrate ZITHROMAC SR Dry Syrup 2g for Adults	Pfizer Japan Inc.	April 6, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 50 Air 120 puffs	GlaxoSmithKline K.K.	April 6, 2009
Minodronic Acid Hydrate Bonoteo Tablets 1mg	Astellas Pharma Inc.	April 7, 2009
Minodronic Acid Hydrate RECALBON Tablets 1mg	Ono Pharmaceutical Co., Ltd.	April 7, 2009

Cetirizine Hydrochloride Zyrtec Dry Syrup 1.25%, Zyrtec tablets 5mg [*1]	UCB Japan Co. Ltd	April 22, 2009
Somatropin (genetical recombination) NORDITROPIN S injection 5mg and 10mg, Norditropin NordiFlex injection 5mg, 10mg and 15mg [*2]	Novo Nordisk Pharma Ltd.	April 22, 2009
Doxorubicin Hydrochloride DOXIL Injection 20mg [*3]	Janssen Pharmaceutical K.K.	April 22, 2009
Sodium Chloride/Potassium Chloride/Sodium Bicarbonate/Anhydrous Sodium Sulfate Niflec for internal use [*4]	Ajinomoto Pharma Co., Ltd.	April 22, 2009
Mosapride Citrate Gasmotin Tablets 2.5 mg and 5 mg, Gasmotin Powder [*5]	Dainippon Sumitomo Pharma Co., Ltd.	April 22, 2009
Sorafenib Tosilate Nexavar Tablets 200mg [*6]	Bayer Yakuhin, Ltd.	May 20, 2009
Valganciclovir Hydrochloride VALIXA Tablets 450mg [*7]	Mitsubishi Tanabe Pharma Corporation	May 20, 2009
Pemetrexed Sodium Hydrate Alimta Injection 500mg [*8]	Eli Lilly Japan K.K.	May 20, 2009
Freeze-dried cell culture derived Japanese encephalitis vaccine Jebik V	The Research Foundation for Microbial diseases of Osaka University	June 2, 2009
Atomoxetine Hydrochloride Strattera capsule 5mg, 10mg, and 25mg	Eli Lilly Japan K.K.	June 19, 2009
Fluticasone Furoate Allermist 27.5μg 56metered Nasal Spray	GlaxoSmithKline K.K.	June 19, 2009
Lapatinib Tosilate Hydrate Tykerb Tablets 250mg	GlaxoSmithKline K.K.	June 19, 2009
Telmisartan, Hydrochlorothiazide Micombi Combination Tablets AP and BP	Nippon Boehringer Ingelheim Co., Ltd.	June 23, 2009
Risperidone RISPERDAL Consta Intramuscular Injection 25mg, 37.5mg, and 50mg	Janssen Pharmaceutical K.K.	June 23, 2009
Insulin Glulisine (Genetical Recombination) APIDRA Inj. Cart, Inj. SoloStar, Inj. 100 units/mL	Sanofi-Aventis K.K	June 24, 2009
Infliximab (Genetical Recombination) REMICADE for I.V. Infusion100 [*9]	Mitsubishi Tanabe Pharma Corporation	July 7, 2009
Etanercept (Genetical Recombination) ENBREL 25mg Syringe for S.C. Injection [*10]	Wyeth K.K.	July 7, 2009
Somatropin (Genetical Recombination) Growject injection 1.33mg, 8mg, BC 8mg [*2]	JCR Pharmaceuticals Co., Ltd.	July 7, 2009
Follitropin alfa (Genetical Recombination) Gonalef 75, Gonalef Pen 450 and 900 [*11]	Merck Serono Co., Ltd.	July 7, 2009
Levofloxacin Hydrate CRAVIT TABLETS 250mg, 500mg, Fine Granules 10%	Daiichi Sankyo Company, Limited.	July 7, 2009
Clozapine CLOZARIL Tablets 25mg, 100mg	Novartis Pharma K.K.	July 29, 2009

Tebipenem Pivoxil ORAPENEM FINE GRANULES 10% FOR PEDIATRIC	Meiji Seika Kaisha, LTD.	August 26, 2009

*1: An additional administration for “pediatrics”
*2: An additional indication for “replacement of endogenous growth hormone in adults with growth hormone hyposecretion (restricted to serious cases)”
*3: An additional indication for “treatment of patients with ovarian cancer whose disease has progressed after chemotherapy”
*4: An additional indication for “cleansing of the colon as a preparation prior to radiographic contrast barium enema”
*5: An additional indication for “adjunction with colonic cleansing agent for a preparation prior to radiographic contrast barium enema”
*6: An additional indication for “treatment of patients with unresctable hepatocellular carcinoma”
*7: An additional indication for “treatment of patients with cytomegalovirus infections associated with Acquired immunodeficiency syndrome, organ transplants (including haemopoietic stem cell transplants), or Malignant tumour”
*8: An additional indication for “treatment of patients with unresctable non-small cell lung cancer recurrent and advanced”
*9: An additional indication for “rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention for structural damage of joints)”
*10: An additional indication for **“**polyarticular-course juvenile idiopathic arthritis (only for cases which are not adequately responsive to conventional therapies)”
*11: An additional indication for “the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders or polycystic ovarian syndrome”

Reference 1. Reports on adverse reactions associated with influenza vaccines in FY 2008 (Conclusion of the Vaccine Adverse Reaction Review Committee)

The reports on adverse reactions associated with influenza vaccines since FY 2003 have been described in Pharmaceuticals and Medical Devices Safety Information. This section summarizes reports on adverse reactions associated with influenza vaccines in FY 2008. **Table 1** indicates the estimated amounts of influenza vaccine shipped, number of adverse reaction reports, and number of adverse reactions cases reported in the past 5 years. **Table 2** shows the number of adverse reactions associated with influenza vaccinations in FY 2008 according to age group, sex, and outcome. A summary and the results of a review of reported cases of death or sequelae in FY 2008 by the Vaccine Adverse Reaction Review Committee, consisting of specialists in infectious diseases and viruses, are shown in **Tables 3 and 4** respectively.

Table 5 shows numbers of adverse reactions reported from influenza vaccinations (reported regardless of causality) in FY 2008 in accordance with the Vaccine Adverse Reaction Reporting System for reference.

Table 1 Estimated amounts of influenza vaccine shipped, reported adverse reaction cases, and adverse reactions reported in the past 5 years

	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Estimated amount of vaccine shipped	Approx. 15.98 million vials	Approx. 19.32 million vials	Approx. 18.77 million vials	Approx. 22.57 million vials	Approx. 24.51 million vials
Number of reported adverse reaction cases	113 cases	102 cases	107 cases	122 cases	121 cases
Number of adverse reaction reported	205 events	139 events	149 events	190 events	166 events

Table 2 Reported cases of adverse reaction associated with influenza vaccination by age group, sex, and outcome

	Total			Recovered/ Improved		Unrecovered		Unknown			Sequelae		Death	
	Male	Female	Sex unknown	Male	Female	Male	Female	Male	Female	Sex unknown	Male	Female	Male	Female
Number of reported cases	121			82		5		27			5 (4)		2 (0)	
	62	57	2	42	40	1	4	15	10	2	3 (2)	2 (2)	1 (0)	1 (0)
Under age of 10	29			22		1		4			1 (1)		1 (0)	
	17	12		13	9		1	3	1		1 (1)			1 (0)
10 to 19 years	17			14				3						
	9	8		6	8			3						
20 to 29 years	6			6										
	1	5		1	5									
30 to 39 years	9			6		1		2						
	6	3		6			1		2					
40 to 49 years	8			5				2			1 (1)			
	5	3		4	1			1	1			1 (1)		
50 to 59 years	10			7				2			1 (1)			
	4	6		2	5			1	1		1 (1)			
60 to 69 years	13			6		1		4			2 (1)			
	3	10		1	5		1	1	3		1 (0)	1 (1)		
70 to 79 years	13			7		1		4					1 (0)	
	7	6		3	4		1	3	1				1 (0)	
80 to 89 years	10			7		1		2						
	8	2		5	2	1		2						
90 to 99 years	2			1				1						
	2			1				1						
Unknown	4			1				3						
		2	2		1				1	2				

(Note) 1. Numbers in parenthesis indicate cases of "Sequelae" and "Death" where causality between the reported adverse reaction and influenza vaccination could not be denied.
2. Counting has overlapped when reported by multiple companies.

Table 3 Summary of death cases

No.	Case summary	Review results of the review committee
1	Female under age of 10 Adverse reactions: encephalopathy Past history/complications: none The patient received the influenza HA vaccination. On the morning 4 days after vaccination the patient had a slight fever of around 37°C. On the evening 5 days after vaccination her level of consciousness started to decrease, she experienced convulsions and was taken to a hospital. She presented with hemorrhage of the digestive tract and hypotension, and saline pumping and gastric irrigation were initiated. A large volume of yellow mucous stool was excreted, she started gasping for air and was intubated and placed on mechanical ventilation. In spite of infusion with sodium bicarbonate and human serum albumin followed by dopamine hydrochloride and dobutamine hydrochloride, cardiac arrest occurred. Heartbeat resumed after cardiac massage and intravenous infusion of adrenaline.	In this case the patient developed symptoms 5 days after vaccination and died 7 days after vaccination. Causality to the influenza vaccination could not be evaluated as the cause of encephalopathy was not identified and information was limited.

	Late at night 5 days after vaccination she developed hypotension. Infusion of fresh frozen human plasma, dry concentrated human antithrombin III, nafamostat mesilate, carbazochrome sodium sulfonate hydrate was initiated but hypotension persisted. Infusion of concentrated human platelet and red cells concentrate was initiated. On the morning 6 days after vaccination a CT examination of the head showed low absorption in the bilateral bridge, midbrain, and thalamus. Mannitol and steroid pulse therapy was initiated. Late at night 6 days after vaccination percutaneous oxygen saturation dropped and an infusion of sivelestat sodium hydrate and milrinone was initiated. On the morning 7 days after vaccination, intratracheal hemorrhage occurred. Cardiac massage was performed for a few minutes for bradycardia. On the afternoon 7 days after vaccination acidosis and intratracheal hemorrhage occurred followed by cardiac and respiratory arrest. The patient died of acute encephalopathy, disseminated intravascular coagulation, and multi-organ failure.	
2	Male in his 70s Adverse reactions: pneumonia, interstitial lung disease, lymphangitis carcinomatosa Past history/complications: rectal cancer, metastatic liver cancer, metastatic lung cancer, cerebral infarction The patient received anticancer drugs half a month before the influenza vaccination. He received the influenza HA vaccination. On the day after vaccination he started to suffer from a feeling of lethargy. 2 days after vaccination he was hospitalized with respiratory failure. 21 days after vaccination he died of respiratory failure associated with lymphangitis carcinomatosa.	In this case the patient developed respiratory failure 2 days after vaccination and died of lymphangitis carcinomatosa 21 days after vaccination. Causality to influenza vaccination could not be evaluated because of limited information on the pneumonia and interstitial lung disease. Lymphangitis carcinomatosa may have been associated with the primary disease and causality to vaccination was denied.

Table 4 Summary of sequelae cases

No.	Case summary	Review results of the review committee
1	Male in his 50s Adverse reactions: Guillain-Barre syndrome Past history/complications: Food allergy The patient received the influenza HA vaccination. He had no history of adverse reactions to vaccinations. 1 month after vaccination a dry, severe cough developed. 2 months after vaccination the patient felt a tingling in his finger tips. 3 days after developing these symptoms he suffered pain in his lower back and slight numbness in his hands. He visited an orthopedist where on examination he was diagnosed as having lumbar spinal stenosis. He received traction and electric therapies and oral drugs were prescribed.	The patient developed symptoms 2 months after vaccination and was diagnosed with Guillain-Barre syndrome. As there were no other suspected causes of neurological symptoms, causality to the influenza vaccination could not be denied.

	30 minutes after a bath at home in the evening of the same day he fell unconscious and stopped breathing. After his airway was secured he resumed spontaneous respiration and recovered consciousness. 4 days after developing symptoms he visited an orthopedist with general paralysis and pain. On CT examination of his lower back cerebral infarction was suspected based on the condition of his lower back. He was hospitalized (for approximately 1 month). 6 days after development of symptoms the symptoms worsened. Spinal fluid was examined in the morning. 7 days after development of symptoms a diagnosis of Guillain-Barre syndrome was made based on the results of examination of the spinal fluid. A first course of high-dose intravenous gamma-globulin therapy was initiated in the evening. 11 days after development of symptoms the first course of high-dose intravenous gamma-globulin therapy was completed. Symptoms improved. 38 days after development of symptoms the patient experienced sudden respiratory discomfort 1 hour after a meal in the morning, oxygen inhalation was initiated. Chest X-ray and ECG tests in the evening showed no abnormalities. A second course of high-dose intravenous gamma-globulin therapy was initiated. 39 days after development of symptoms his respiratory status improved slightly in the early morning. 42 days after development of symptoms the second course of high-dose intravenous gamma-globulin therapy was completed. 137 days after development of symptoms the patient began rehabilitation (for 2 months and 3 weeks). 213 days after development of symptoms paralysis remained in 10% of his face, the area around his mouth felt strange, with more severe paralysis on the right cheek compared to the left. 221 days after development of symptoms he was discharged with sequelae of Guillain-Barre syndrome (numbness on the soles of his feet and paralysis in the right side of the face). 747 days after development of symptoms a slight paralysis remained in the right side of the face, his voice turned hoarse when his muscles were tired, and there was a strange sensation that the soles of his feet felt like they were stepping on bubble-wrap packing material. He has now returned to a normal life in spite of mild sequelae (numbness in the soles of his feet and paralysis in the right side of the face).	
2	Female in her 40s Adverse reactions: Guillain-Barre syndrome Past history/complications: none The patient received the influenza HA vaccination. On the day after vaccination she developed a	In this case the patient developed symptoms 2 days after vaccination and was diagnosed as having Guillain-Barre syndrome 8 days after vaccination. Although some laboratory findings were open to question, the clinical course indicated that the possibility of Guillain-Barre syndrome and causality

	pyrexia. 2 days after vaccination severe arthralgia developed in the upper limbs. 3 days after vaccination the patient presented with general lethargy and severe arthralgia. Posterior cervical pain and lower abdominal pain also developed after examination. 5 days after vaccination she developed dysuria. 6 days after vaccination facial hypoesthesia and bulbar palsy developed. 8 days after vaccination she developed cerebellar ataxia, absent deep tendon reflex, and abasia. She was diagnosed with Guillain-Barre syndrome. An infusion of human immunoglobulin was initiated. 23 days after vaccination 3-day plasmapheresis was initiated, which did not achieve an alleviation of neurological symptoms. Between 1 month and 2 months after vaccination parenteral nutrition was performed for abdominal pain, diarrhea, and vomiting. 140 days after vaccination mechanical ventilation was performed for 3 days to treat dyspnea and sputum excretion difficulty. Acetaminophen, nonsteroidal anti-inflammatory drugs, and pentazocine had been administered without success since the early stage of the symptoms to treat intermittent lower abdominal pain. Oral morphine did not control the pain. 546 days after vaccination an epidural block was performed with little success. The patient has since been on multiple medications with a poor outcome.	to the influenza vaccination could not be denied.
3	Female in her 60s Adverse reactions: Guillain-Barre syndrome Past history/complications: none The patient received the influenza HA vaccination. 9 days after vaccination she developed a swinging gait and diplopia. 10 days after vaccination the patient was hospitalized with aggravated symptoms. 11 days after vaccination total external ophthalmoplegia and facial palsy developed. High-dose intravenous gamma-globulin therapy was initiated. 12 days after vaccination she developed bulbar palsy, respiratory muscle paralysis, and quadriplegia. The symptoms exacerbated and mechanical ventilation was initiated. 39 days after vaccination a tracheostomy was performed with ventilator weaning. Bulbar palsy remained. 82 days after vaccination gastrostomy was performed. 128 days after vaccination the patient was able to walk but her gait was unstable due to ataxia. She was unable to raise her hands because of paralysis in the upper limbs. Speech was audible but impaired. 132 days after vaccination she was transferred to another hospital for rehabilitation. 219 days after vaccination she was transferred to the initial hospital for recuperation.	Given that symptoms developed 9 days after vaccination and there were no other suspected causes of the neurological symptoms, causality to the influenza vaccination could not be denied.

	269 days after vaccination she was discharged. Symptoms (facial palsy and limb ataxia) remained but she recovered the ability to carry out activities of daily living.	
4	Male under age of 10 Adverse reactions: acute disseminated encephalomyelitis Past history/complications: none The patient received the influenza HA vaccination. 19 days after vaccination he had developed a pyrexia. On the afternoon 21 days after vaccination he suffered convulsions. He staggered, hit a door and fell and hit the back of his head. He did not feel well after this happened. His level of consciousness gradually decreased and he fell asleep. 26 days after vaccination he visited a hospital and was examined. 27 days after vaccination after an examination his consciousness level decreased. An MRI examination showed high signal intensity in the bridge and total white matter signal intensity. The pupils had no light reflex. He did not respond to stimulation and remained unconscious. He was hospitalized with acute encephalitis. On the same day, a first course of steroid pulse therapy was performed. 35 days after vaccination a second course of steroid pulse therapy was performed. 45 days after vaccination a third course of steroid pulse therapy was performed, after which his condition improved. Date unknown, he was negative for human herpesvirus 6 and herpes simplex virus on PCR assays. A final diagnosis of acute disseminated encephalomyelitis was made based on the clinical course and therapeutic effects. 77 days after vaccination he was discharged and has since been followed up as an outpatient. He is currently under rehabilitation for movement, mental, and language disorders.	Given that symptoms developed 19 days after vaccination and there were no other suspected causes of the neurological symptoms, causality to the influenza vaccination could not be denied.
5	Male in his 60s Adverse reactions: muscular weakness, nausea Past history/complications: type 2 diabetes, hypertension, lacunar infarction, thermal urticaria, eczema Rosuvastatin calcium was prescribed to treat dyslipidemia. After approximately 1 month's treatment with rosuvastatin calcium the patient's urine was brown and he felt listless. After 80 days' treatment with rosuvastatin calcium his medication was switched from rosuvastatin calcium to ezetimibe during a routine visit. Other oral drugs were also prescribed. The patient received the influenza HA vaccination. There were no immediate side effects and he returned home. On the day after vaccination he developed a general lethargy, weakness of the lower limbs, and queasy.	Symptoms developed as early as 1 day after vaccination and may have been associated with concomitant medications or an underling disease. However, since details are unknown and information is limited, causality to the influenza vaccination could not be evaluated.

	4 days after vaccination he visited the hospital. He was able to walk and was lucid but was weak in his lower limbs. Replacement fluid, nizatidine, and domperidone were prescribed to treat queasy. 8 days after vaccination the patient presented with persisting weakness in his lower limbs. Based on examination results and the clinical course he was diagnosed as having Guillain-Barre-like symptoms following the influenza HA vaccination. He took medication with mecobalamin for the underlying disease and decided to be followed up. 20 days after vaccination the patient was weak in the lower limbs and unable to walk with his heels touching the floor. Symptoms remained unchanged in severity. Follow-up continued with medication with mecobalamin. 55 days after vaccination the symptoms had gradually improved but weakness of the lower limbs had not fully recovered.	

Table 5 Reports of adverse reactions associated with influenza vaccines in FY 2008 (reported regardless of causality)

	Total	Recovery	Death	Serious	Hospitalization	Sequelae	Other	N/A
Total	55	33	2		3		11	6
1. Immediate systemic reaction	9	8						1
1A. Anaphylaxis								
1B. Systemic urticaria	9	8						1
2. Encephalitis, encephalopathy								
3. Convulsion								
4. Movement disorder								
5. Other neurological disorders	2	1			1			
6. Local abnormal swelling (over the elbow)	1						1	
7. Generalized rash								
8. Pyrexia of 39°C and more	8	5					2	1
9. Other abnormal reactions	9	9						
10. Nonstandard reports	26	10	2		2		8	4
10A. Local reaction (redness, swelling, etc.)	18	8					8	2
10B. Systemic reaction (pyrexia etc.)	1	1						
10C. Other	7	1	2		2			2

(Note) 1. Listed figures are provisional and subject to future change.
2. The Vaccine Adverse Reaction Reporting System is intended, based on Immunization Practices, to collect and provide the public with information on changes in the health of individuals who have been vaccinated as required by the Preventive Vaccination Law. This reporting system is limited to those individuals who receive routine vaccinations.