Pharmaceuticals and Medical Devices Safety Information

No. 251 October 2008

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

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

Pharmaceuticals and Medical Devices Safety Information

No. 251 October 2008

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

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

Adverse Drug Reaction Relief System and Relief System for Infections Derived from Biological Products

1. Introduction

Pharmaceuticals are indispensable for maintaining human health and welfare. However, in some cases, onset of adverse reactions from such pharmaceuticals cannot be prevented, even if proper care is exercised. In addition, it is extremely difficult to completely prevent infection hazards from biological products, even if safety measures based on the latest scientific knowledge are taken.

"Adverse Drug Reaction Relief System" is established for the purpose of relieving people suffered from adverse health effects such as diseases or disabilities that were caused by adverse reactions of pharmaceuticals, even if such pharmaceuticals were properly used, in the manners of prompt and simple procedure. This is a public service funded by contributions etc. made by marketing authorisation holders of pharmaceuticals and biological products to fulfill their social responsibilities. More than a quarter of the century has passed since the establishment in 1980. Until now, more than 7400 people have been granted relief benefits.

In 2004, "Relief System for Infections Derived from Biological Products", which is also a public service, was established for the purpose of relieving people suffering from adverse health effects such as infectious diseases or disabilities that were caused by biological products, even if such biological products were properly used, in the manners of prompt and simple procedure.

Please refer to the Pharmaceuticals and Medical Devices Agency (hereafter, the PMDA) website (http://www.pmda.go.jp/kenkouhigai.html, in Japanese) (videos available) for details of these services.

Recently, the number of applications for adverse health effects relief system (refers to Adverse Drug Reaction Relief System and Relief System for Infections Derived from Biological Products, the same shall apply hereafter) is on the increase. However, it has been pointed out that dissemination of the system is still not enough. In addition, the coverage of this service was extended to include the sufferings of adverse reactions from interferon products (in case of use for chronic hepatitis B, chronic hepatitis C, etc.) since April this year. Based on the above, claims for relief benefits, etc. (information to be provided to health effects suffers) and examples of cases eligible for relief benefit etc. are presented for the purpose of further application of the service by people suffered from adverse health effects.

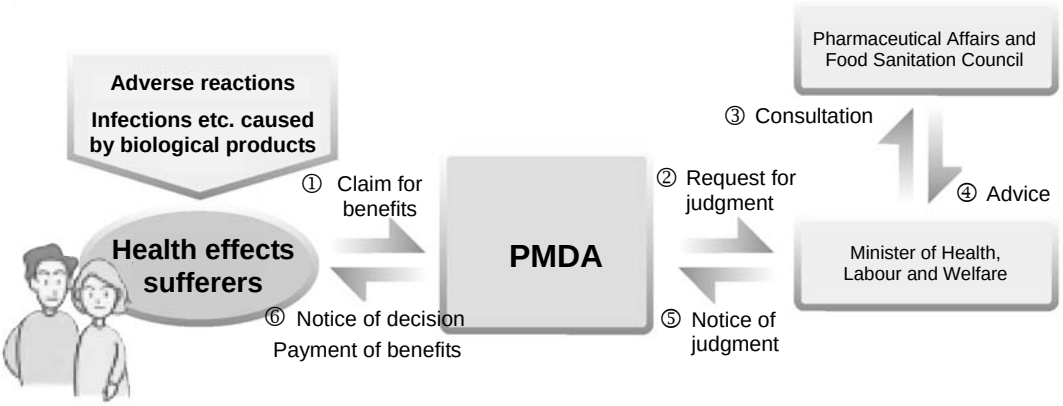
2. Claims for relief benefits, etc. (information to be provided to health effects sufferers)

When healthcare providers obtained information on possible adverse health effects caused by the use of pharmaceuticals or biological products from patients etc. by way of medical consultation, they should provide information on this service and the following points to the people suffered from adverse health effects or their bereaved family.

(1) Method of claim for relief benefits

The claims for relief benefits should be submitted directly to the PMDA by the patient suffering from health damages caused by adverse reactions or infections, or by his/her bereaved family (hereafter claimants).

Flowchart of relief service



* Any person who is not satisfied with the judgment on eligibility for relief benefits (payment/non-payment) may request for reconsideration to the Minister of the MHLW.

(2) Types of benefits and dead line for claim etc.

There are the following 7 different types of benefit: Medical Expenses, Medical Allowances, Disability Pension, Pension for Raising Handicapped Children, Bereaved Family Pension, Lump-sum Benefits for Bereaved Family, and Funeral Expenses (For the details of each benefit and due for claim etc., refer to pages 8 to 10 of **Document 1**).

(3) Documents required for claims

○ Physician's certificate ○ Certificate of prescription ○ Certificate of medical examination, etc.

When receiving relief benefit, it is necessary to prove the pathogeny and symptoms/progress of the adverse reaction and infection, and that they resulted from the use of pharmaceuticals, etc.

Therefore, in claiming a relief benefit, a medical certificate from the physician who conducted treatment for the health hazards from adverse reactions or infections as well as proof of prescription become necessary, or proof of purchase if the drug was bought from pharmacies etc. and claimants should request their physician to create these certificates and submit them to the PMDA together with the claim form filled out by the claimant.

All forms, including claim forms and medical certificates, are available from the PMDA, and can be sent free of charge upon request by claimants. The necessary documents can also be downloaded from the PMDA's website (visit http://www.pmda.go.jp/kenkouhigai/fukusayo_dl/ for Adverse Drug Reaction Relief System; for Relief System for Infections Derived from Biological Products, visit http://www.pmda.go.jp/kenkouhigai/kansen_dl/).

(4) Reference for adverse health effects relief system

The documents required in claiming the relief benefit include a written request according to the type of benefits, a diagnosis form, a proof of medical examination, and a proof of prescription. In claiming the relief benefit, please contact "Relief System Consultation Service" within the PMDA by phone or E-mail in advance.

Pharmaceuticals and Medical Devices Agency
(Relief System Consultation Service)
Telephone: 0120-149-931 (a toll-free number)
Operating hours: [Monday to Friday] 9:00-17:30 (excluding national holidays and New Year holidays)
Email: kyufu@pmda.go.jp
Website: http://www.pmda.go.jp/kenkouhigai.html (in Japanese)

3. Examples of cases of payment of relief benefits etc.

(1) Cases of payment of relief benefits

In this part, particular cases of payment of relief benefit are presented.

In addition, details of the cases of payment/non-payment of adverse reaction relief benefits [name of drug (brand name), name etc. of the adverse reaction, description of the benefit, reason for non-payment, etc.] are announce on the Pharmaceuticals and Medical Devices Agency's website (http://www.pmda.go.jp/kenkouhigai/help/information.html, in Japanese).

[Medical Expenses/Medical Allowances]

<Oculomucocutaneous syndrome>

Female in 50s. The patient was prescribed loxoprofen sodium for the treatment of pain in the right elbow. When the patient received another consultation for persisted pain, she was diagnosed with gout and prescribed allopurinol. After 14 days, as blood blister in mouth, itching of eyes and vulva, and pyrexia developed, the administration was discontinued. On the following day, as there were itching on the torso, onset of conjunctival hyperaemia, and increase in an amount of eye discharge, the patient visited the hospital the next day. Erythema oedematous was observed and the patient was diagnosed with oculomucocutaneous syndrome. She was hospitalized for treatment for approximately 5 weeks.

[Disability Pension/Pension for Raising Handicapped Children]

<Drug-induced renal impairment>

Female in 60s. The patient had been administrated omeprazole prescribed for reflux oesophagitis, and loxoprofen sodium prescribed for right lymph nodes cervical swollen, pain, and pyrexia. Creatinine level was gradually increased, and an emergency dialysis was implemented for drug-induced renal impairment. However, renal function did not recover and maintenance dialysis was started.

[Bereaved Family Pension/Lump-sum Benefits for Bereaved Family/Funeral Expenses]

<Anaphylactic shock (anaphylactoid symptoms)>

Female in 70s. Intramuscular injection of glucagon was performed for the pretreatment of gastroscopy. 1 minute after the injection, she collapsed from her chair immediately after the patient put lidocaine hydrochloride in her mouth. Loss of consciousness, respiratory arrest, and pulse weak developed. Vascular access, cardiac massage, artificial respiration, intravenous injection of epinephrine, and intratracheal intubation were conducted. After that, although sinus rhythm was restored, the patient became comatose and transferred to ICU (intensive care unit). Although artificial respiration and administration of intravenous vasopressor were continued, the patient died.

(2) Examples of cases not eligible for relief benefits

Until now, more than 7400 people have been granted relief benefits. On the other hand, decision of non-payment has been made for more than 1200 people.

The following cases are not eligible for adverse health effects relief system:

a. Cases of adverse health effects resulting from statutory vaccination (Relief System for Injury Health with vaccinations) available for such cases). However, cases of adverse health effects resulting from voluntary vaccinations are eligible for relief benefits.
b. When the liability for damage by others such as the marketing authorisation holder of the pharmaceutical or biological product is clear.
c. Cases where it was necessary to use the pharmaceutical or biological product in an amount exceeding the regular dosage for the purpose of saving the patient's life, even if it was acknowledged beforehand that adverse health effects may occur.
d. Cases where the pharmaceutical or biological product was not intended to be used properly or not used properly.

e. Cases of adverse health effects caused by pharmaceuticals not applicable to relief benefits.

The pharmaceuticals not applicable to relief benefits include:

① Pharmaceuticals used for the purpose of the treatment of cancer or other specific diseases designated by the Minister of Health, Labour and Welfare (anticancer drugs and immunosuppressant, etc.).

② Pharmaceuticals that may not cause sufferings of adverse reactions such as pharmaceuticals not directly used for human bodies or pharmaceuticals without pharmacological action (insecticides, antimicrobial agents, and IVDs, etc.).

○ Interferon alfa products (injectable dosage form used for the treatment of chronic hepatitis B, chronic hepatitis C, or compensated cirrhosis in progression of chronic hepatitis C)
○ Interferon beta products (injectable dosage form used for the treatment of chronic hepatitis B, chronic hepatitis C, or compensated cirrhosis in progression of chronic hepatitis C)
○ Peg-Interferon alfa products
○ Ribavirin products

Ribavirin products had been previously included in the pharmaceuticals not applicable to relief benefits of ① above. On April 1, 2008, ribavirin products were excluded from the category ① and became eligible for relief benefits. However, cases of adverse health effects resulting from the use of ribavirin products other than the purpose indicated in ( ) are still not eligible for relief benefits.

Relief benefits are applicable to sufferings of adverse reactions caused by interferon products that were administrated on and after April 2008 [However, the sufferings of adverse reactions caused by interferon alfa products (injectable dosage form used for the treatment of compensated cirrhosis in progression of chronic hepatitis C) that were administrated on and after October 16, 2008 were applicable for relief benefits]. Please contact the PMDA for more details.

f. Cases of mild adverse health effects (when the claimant did not receive the required extent of medical treatment in cases requiring hospitalization), or where the period for claiming relief benefits has passed.

Breakdown etc. of cases not eligible for relief benefits in FY2007 are indicated (refer to pages 10 to 11 of **Document 2**).

As the reasons for decision of non-payment, “No causality” and “Not applicable to adverse health effects requiring hospitalization or grade of disability” were account for more than 70% of all non-payment cases. In cases where causality with the adverse health effects and the pharmaceuticals is not confirmed or the required extent of medical treatment was not given even if the pharmaceuticals were used, are not eligible for relief benefits.

In addition, there were cases where “Pharmaceuticals or biological products were used for unapproved indications or not used properly” accounted for approximately 20% of all non-payment cases. Generally in cases where pharmaceuticals or biological products were used without following the PRECAUTIONS section in the package inserts may not eligible for relief benefits of this system even if adverse health effects occur. Such use is also serious problem from the standpoint of prevention of possible health hazards caused by the use of pharmaceuticals, etc.

4. Closing comments

Understanding and cooperation from healthcare professionals including physicians and pharmacists is essential for relieving health effects suffers by the adverse health effects relief system.

As mentioned in the opening sentences, adverse reactions etc. from pharmaceuticals etc. cannot be prevented in some cases, even if proper care is exercised. Therefore, relief of adverse health suffers from such adverse reactions should be implemented in the manners of prompt and simple procedure of this system apart from the extent of civil liabilities. Some of healthcare professionals are not willing to prepare diagnosis forms, etc. required for claim of relief benefits, because they misunderstand that the preparations

of such documents lead to admit that the health adverse effect was caused by their inappropriate medical practice. However, the purpose of this service is to promptly relief people suffering from adverse health effects caused by pharmaceuticals etc. Therefore, the documents provided by healthcare professionals such as diagnosis forms have an important role in making decision regarding relief benefits.

As mentioned in the section 2, in cases where adverse reactions, etc. occur, or when healthcare providers become aware of the onset of adverse reactions, etc. or asked for consultation from patients, etc. about the adverse reactions, etc. possibly eligible for this relief benefits, they should provide information on this service to the patients. In addition, the PMDA asks for your continued corporation in preparing documents required for claims of relief benefits such as diagnosis forms.

Document 1. Details of benefits and due for claim, etc. of adverse health effects relief system

In cases of disease (requiring hospitalization)

Medical Expenses

Compensation will reflect the actual costs of treatment of the diseases caused by the adverse reactions of pharmaceuticals, etc. borne by the patient.

The coverage of Medical Expenses includes treatment for diseases requiring hospitalization, which is caused by the adverse reactions of pharmaceuticals, etc., and those similar extents of treatments are required. The disease requiring hospitalization will not necessarily limit to the cases where the patient was actually hospitalized. Patient with home treatment due to circumstances beyond control can also be eligible for Medical Expenses, if the condition is considered as having similar degree of diseases requiring hospitalization.

[Due for claim] Within 2 years since the payment of costs eligible for Medical Expenses (however, for the costs that were paid on and after May 1, 2008, the claim should be made within 5 years).

[Claimant] The person who received treatment for diseases caused by adverse reactions, etc.

Medical Allowances

Relief is provided for costs other than medical costs (round-trip transportation expenses to hospital, miscellaneous expenses accompanying hospitalization, etc.) for treatment of disease caused by adverse reactions of pharmaceuticals, etc. The coverage of Medical Expenses includes the treatment for diseases requiring hospitalization, similar to the coverage of Medical Expenses, in principle.

Medical Allowances are paid by monthly units. Amount of payment as of April 1, 2008 is as follows:

(In cases with outpatient treatment only)	
Cases with 3 days and more of outpatient treatments a month	35800 yen (monthly amount)
Cases with less than 3 days of outpatient treatments a month	33800 yen (monthly amount)
(In cases with hospitalization only)	
Cases with 8 days and more of outpatient treatments a month	35800 yen (monthly amount)
Cases with less than 8 days of outpatient treatments a month	33800 yen (monthly amount)
(In cases with hospitalization and outpatient treatments)	35800 yen (monthly amount)

[Due for claim] Within 2 years since the first day of next month of the month the payment of costs eligible for Medical Allowances are made. (however, for the treatment that were given on and after May 1, 2008, due for claim is within 5 years)

[Claimant] The person who received treatment for diseases caused by adverse reactions, etc.

In cases of a certain degree of disability (causing serious impairment in daily life)

Disability Pension

Relief is provided to compensate living costs, etc. of patients aged 18 and older, who suffer from a certain degree of disability caused by adverse reaction, etc. of pharmaceuticals.

The degree of disability is classified as Grade 1 and Grade 2. The outline is as follows:

① Grade 1: Persons without abilities to perform activities of daily life due to disability
(Patients who need full assistance in daily life)

② Grade 2: Persons with serious impairment in daily life or persons who should be imposed strict limits
(Patients with serious impairment in daily life who is not always need assistance in daily life)

Amount of payment as of April 1, 2008 is as follows:

① Grade 1: 2720400 yen (annual amount) (monthly amount: 226700 yen)
② Grade 2: 2175600 yen (annual amount) (monthly amount: 181300 yen)

[Due for claim] No definite deadline is established.
[Claimant] Persons with disability caused by adverse reactions, etc. (aged 18 and older)

Pension for Raising Handicapped Children

Relief is provided for those who are responsible for raising children under age of 18 who suffer from a certain degree of disability caused by adverse reactions of pharmaceuticals, etc.

Person who is responsible for raising a handicapped child refers to persons generally accepted as raising the child by comprehensively considering that the person is living with the children and supporting livelihood. The degree of disability is similar to that of Disability Pension.

Amount of payment as of April 1, 2008 is as follows:

① Grade 1: 850800 yen (annual amount) (monthly amount: 70900 yen)
② Grade 2: 680400 yen (annual amount) (monthly amount: 56700 yen)

[Due for claim] No definite deadline is established.
[Claimant] Person who is responsible for raising children with disabilities caused by adverse reactions, etc.

In cases of death

Bereaved Family Pension

Relief is provided for bereaved families in rebuilding their life following the death of their main provider from the adverse reactions of pharmaceuticals, etc.

The maximum period for payment of Bereaved Family Pension is 10 years. Amount of payment as of April 1, 2008 is 2378400 yen (annual amount) (monthly amount: 198200 yen).

[Due for claim] 5 years within death.
However, in cases where Medical Expenses, Medical Allowances, Disability Pension, or Pension for Raising Handicapped Children has decided to be granted, the claim should be made within 2 years since the death.
[Claimant] Persons with the highest priority in bereaved family who is within the same household with the person (main provider) who died from adverse reactions, etc.
The order of priority is ① a spouse, ② child, ③, father or mother ④ grandchild, ⑤ grandfather or grandmother, and ⑥ brother or sister (a spouse includes persons in similar circumstances as a registered marriage).

Lump-sum Benefits for Bereaved Family

Relief is provided for bereaved families as a gesture of sympathy following the death from adverse reactions of pharmaceuticals, etc. of their family member who is not the main provider.

Lump-sum Benefits for Bereaved Family are paid by 36 months of Bereaved Family Pension. Amount of payment as of April 1, 2008 is 7135200 yen.

[Due for claim] Same as those of Bereaved Family Pension.
[Claimant] A person with the highest priority in bereaved family who is within the same household with the person (other than main provider) who died from adverse reactions, etc. (For the order of priority, refer to the section of Bereaved Family Pension)

Funeral Expenses

Relief is provided for costs in holding a funeral for the person who died from adverse reactions of pharmaceuticals, etc. to the person who holds the funeral.

Amount of payment as of April 1, 2008 is 199000 yen.

[Due for claim] Same as those of Bereaved Family Pension.
[Claimant] A person who held the funeral of the person died from adverse reaction, etc.

Document 2. Cases not eligible for relief benefits

In this section, cases not eligible for relief benefits (non payment) in the Adverse Drug Reaction Relief System are presented.

The number of non-payment accounted for approximately 16% of all claims in FY2007 (a total number of payment and non-payment is 855. Of these, cases of non-payment accounted for 135).

The reasons for non-payment (FY2007) are "No causality" (46.7%), "Not applicable to adverse health effects requiring hospitalization or grade of disability" (25.9%), "Pharmaceuticals or biological products were not intended to be used properly or not used properly" (20.7%), "Pharmaceuticals not applicable to relief benefits" (2.2%), "Impossible to judge" (1.5%), and "Others" (3%).

No causality

"No causality" refers to cases in which the disease or disability is not likely to be caused by adverse reactions of pharmaceuticals.

Not applicable to adverse health effects requiring hospitalization or grade of disability

"Not applicable to adverse health effects requiring hospitalization or grade of disability" refers to the cases in which although the causality between pharmaceuticals and the disease is confirmed, the required extent of medical treatment for the disease requiring hospitalization is not given or the degree of the disability is not applicable to "Persons without abilities to perform activities of daily life due to disability (Grade 1)" or "Persons with serious impairment in daily life (Grade 2)".

Generally, the cases with outpatient treatment alone are not eligible for relief benefits.

Pharmaceuticals or biological products were not intended to be used properly or not used properly

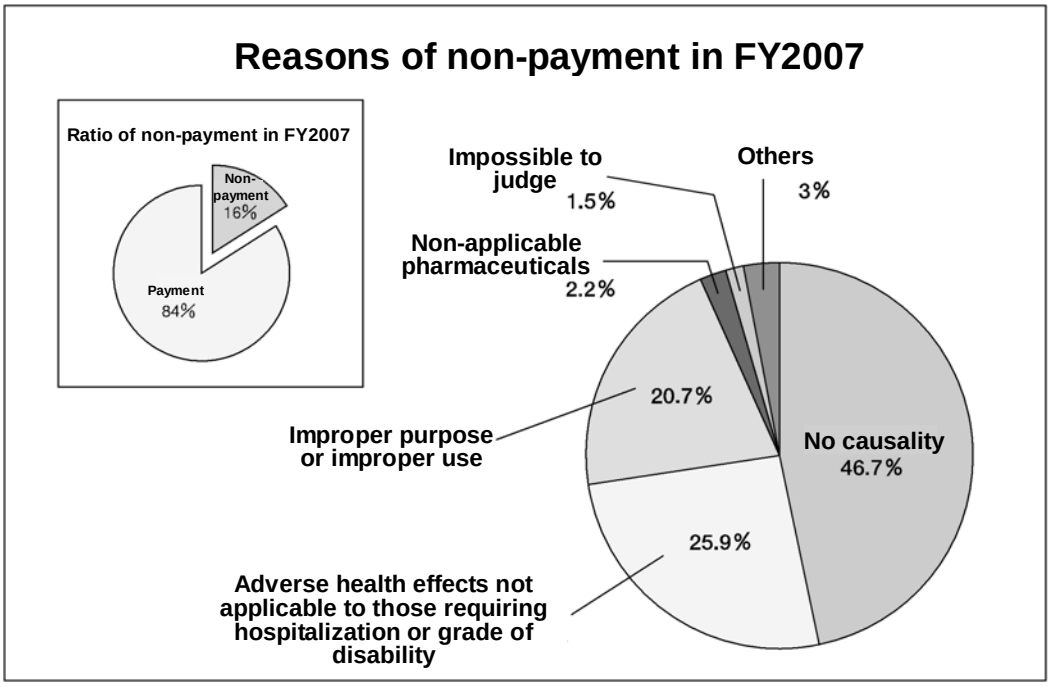
"Pharmaceuticals or biological products were not intended to be used properly or not used properly" includes the cases where the causative pharmaceuticals of adverse health effects from adverse reactions are used for the indications other than those approved by the Minister of the MHLW, or where the pharmaceuticals are used without following the PRECAUTION section in the package inserts.

The following cases are considered as an improper use. The adverse health effects are not eligible for relief benefits in such cases.

- In cases where necessary tests were not conducted without proper justification despite there was description of "For at least 2 months after initiating administration, physicians should be particularly alerted to the emergence of initial symptoms of the adverse reactions. In principle, blood count (including differential leukocyte count) and hepatic function tests should be performed once every 2 weeks…" in the PRECAUTIONS section in the package insert.
- In cases where the OTC drugs such as common cold drugs or antipyretics and analgesics are concomitantly used with the other pharmaceuticals, which are prohibited by the package insert.

"PRECAUTIONS" originally includes necessary information in order to ensure safety of patients who use pharmaceuticals for the purpose of proper use. However, please note that adverse health effects relief system may not be applied to the cases of health adverse effects resulted from the use without following the PRECAUTIONS section in the package inserts.

In addition, in the cases of adverse reactions in which the pharmaceuticals being left without used (so called "unused drug") are taken by patient's self-judgment without instruction of physicians are generally not eligible for relief benefits as such cases are considered as an improper use.



Pharmaceuticals not applicable to relief benefits

"Pharmaceuticals not applicable to relief benefits" refers to the cases where the pharmaceuticals not applicable to relief benefits are included in the causative drug.

Impossible to judge

"Impossible to judge" refers to the cases where causality or proper purpose/proper use cannot be judged, as the submitted documents are insufficient.

2

Airway clogging of heat and moisture exchangers due to use in combination with heated humidifier

1. Outline

The Japan Council for Quality Health Care currently reported the cases of combination use of heat and moisture exchangers and heated humidifier collected in their project for report on potentially dangerous minor incidents as shown in the following table. The detail of those cases can be available on the Council's website (http://jcqhc.or.jp/html/index.htm, in Japanese).

No.	Detail	Background and factor	Measure
7	A heated humidifier had been used for the purpose of expectorant in the patient with mechanical ventilator over long time periods. Although water was frequently discharged from the water-trap to drain moisture from breathing circuit during the night, after shift change, a physician discovered the heat and moisture exchangers placed in the circuit.	Heat and moisture exchangers were placed in the circuit while using a heated humidifier due to the lack of knowledge for functions of heat and moisture exchangers. The other medical staff did not notice the heat and moisture exchangers placed in the circuit although the staff monitored the circuit and used to heat and moisture exchangers.	· Function and necessity of each device should be reconfirmed.

Extract from "Figure III-10. Examples of potentially dangerous minor incidents (mechanical ventilator) in 10th report of the medical accident and incident report project"

Heat and moisture exchangers (excluding the types of heat and moisture exchangers for patients with tracheotomy which cannot be connected to an mechanical ventilator; the same shall apply hereafter) is an apparatus heating and humidifying inspired gas using heat and moisture captured from each exhaled breath (refer to **Figure 1**). On the other hand, a heated humidifier is an apparatus heating and humidifying the gas from mechanical ventilator, etc. inside the circuit of patients (refer to **Figure 2**). When the heat and moisture exchangers are used in combination with heated humidifier, there are risks of increase in flow resistance due to excessive moisture absorption of heat and moisture exchangers and airway clogging of heat and moisture exchangers (refer to **Figure 3**). In addition, there is also risk of a low-pressure alarm is not activated in the case of displacement or leakage of circuit depending on the low-pressure alarm setting of mechanical ventilator, etc.

In response, the package insert of these medical devices were investigated. As the result, there were package inserts without descriptions of combination use of the heated humidifier and heat and moisture exchangers in "CONTRAINDICATIONS" section. In some package inserts, although there was the description in "Contraindications for concomitant use", the reasons for the contraindication such as a risk of an airway clogging were not specified.

For this reason, the notification has been issued dated on September 11, 2008 to the marketing authorisation holders of those medical devices to inspect package inserts, to revise the package inserts according to the result of their self-inspection, and to call for attention of medical institutions by providing information, including proper usage and the aforementioned risks.

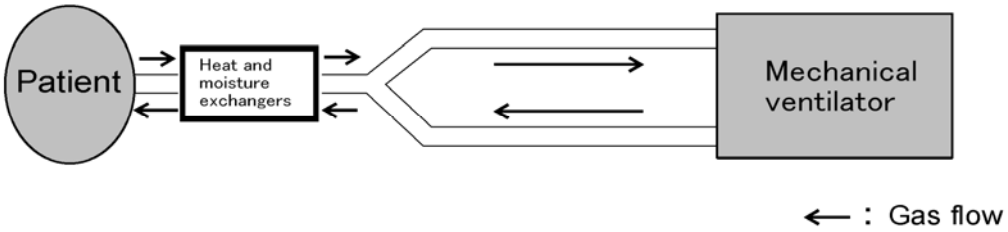


Figure 1. Chart of breathig circuit of mechanical ventilator with heat and moisture exchangers (example of proper circuit)

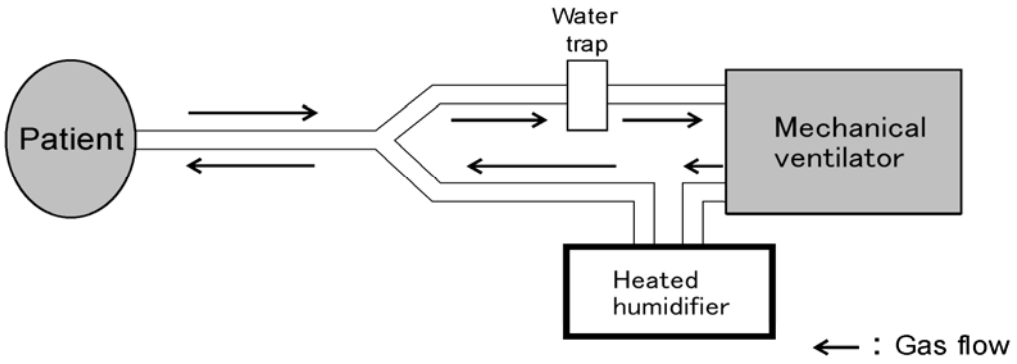


Figure 2. Chart of breathig circuit of mechanical ventilator with heated humidifier (example of proper circuit)

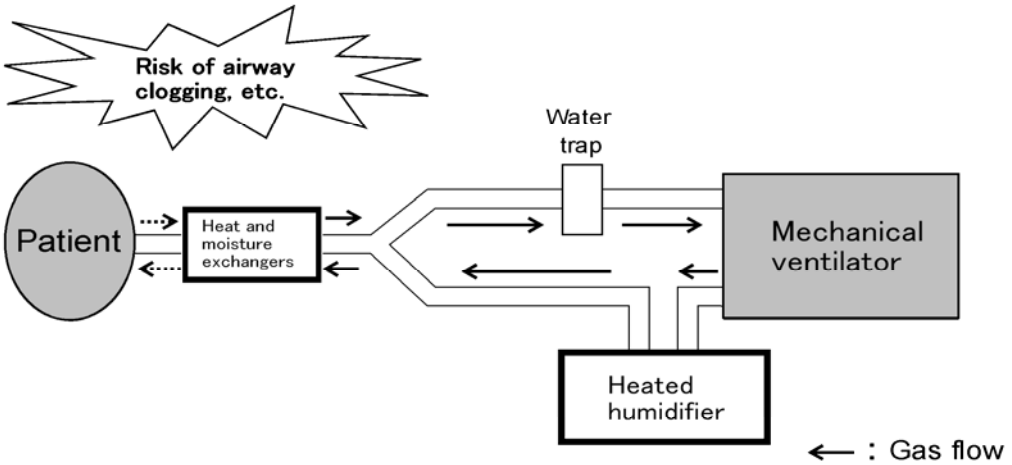


Figure 3. Chart of breathig circuit of mechanical ventilator with heated humidifier and heat and moisture exchangers (example of improper circuit)

* There are risks of increase in flow resistance due to excessive moisture absorption of heat and moisture exchangers and airway clogging of heat and moisture exchangers.

2. Contents of package insert

(1) Heat and moisture exchangers or mechanical ventilator/anesthesia machine, etc. equipped with heat and moisture exchangers

"Contraindications for concomitant use" section

Descriptions of "heated humidifier" and "In case of combination use with heated humidifier, airway clogging of filter inside heat and moisture exchangers may occur and making it difficult to ventilate." should be added in the section.

(2) Heated humidifier or mechanical ventilator/anesthesia machine, etc. equipped with humidification chamber of heated humidifier

"Contraindications for concomitant use" section

Descriptions of "heat and moisture exchangers" and "In case of combination use with heated humidifier, airway clogging of filter inside heat and moisture exchangers may occur and making it difficult to ventilate." should be added in the section.

3. Request to healthcare providers

Healthcare providers should carefully read the package insert of medical devices and confirm proper use of each medical device in use.

3

List of products subject to Early Post-marketing Phase Vigilance

(As of October 1, 2008)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Montelukast Sodium Kipres Tablets 10[*1]	Kyorin Pharmaceutical Co., Ltd.	January 25, 2008
Montelukast Sodium Singulair Tablets 10 mg[*1]	Banyu Pharmaceutical Co., Ltd.	January 25, 2008
Sorafenib Tosilate Nexavar 200 mg	Bayer Yakuhin, Ltd.	February 25, 2008
Galsulfase (Genetical recombination) Naglazyme for Intravenous Infusion 5 mg	AnGes MG, Inc.	April 14, 2008
Tocilizumab (Genetical recombination) Actemra 200 for Intravenous Infusion[*2]	Chugai Pharmaceutical Co., Ltd.	April 16, 2008
Sildenafil Citrate Revatio Tablets 20 mg	Pfizer Japan Inc.	April 18, 2008
Naratriptan Hydrochloride Amerge Tablets 2.5 mg	GlaxoSmithKline K.K.	April 18, 2008
Montelukast Sodium Kipres Tablets 5 mg	Kyorin Pharmaceutical Co., Ltd.	April 18, 2008
Montelukast Sodium Singulair Tablets 5 mg	Banyu Pharmaceutical Co., Ltd.	April 18, 2008
Zinc Acetate Dihydrate Nobelzin Capsules 25 mg and 50 mg	Nobelpharma Co., Ltd.	April 22, 2008
Blonanserin Lonasen Tablets 2 mg and 4 mg, Lonasen Powder 2%	Dainippon Sumitomo Pharma Co., Ltd.	April 22, 2008
Enoxaparin Sodium Clexane for Subcutaneous Injection Kit 2000 IU	Sanofi-Aventis K.K.	April 24, 2008
Varenicline Tartrate Champix Tablets 0.5 mg and 1 mg	Pfizer Japan Inc.	May 8, 2008
— Artcereb Irrigation and Perfusion Solution for Cerebrospinal Surgery	Otsuka Pharmaceutical Factory, Inc.	May 12, 2008
Thrombomodulin Alfa (Genetical recombination) Recomodulin Inj.12800	Asahi Kasei Pharma Corporation	May 12, 2008
Human Serum Albumin (Genetical recombination) Medway Injection 25% and 5%	Mitsubishi Tanabe Pharma Corporation	May 19, 2008
Tacrolimus Hydrate Talymus Ophthalmic Suspension 0.1%	Senju Pharmaceutical Co., Ltd.	May 20, 2008
Fondaparinux Sodium Arixtra Injection 1.5 mg and 2.5 mg[*3]	GlaxoSmithKline K.K.	May 20, 2008

Sitafloxacin Hydrate Gracevit Tablets 50 mg, Gracevit Fine Granules 10%	Daiichi Sankyo Co., Ltd.	June 2, 2008
Sunitinib Malate Sutent Capsule 12.5 mg	Pfizer Japan Inc.	June 13, 2008
Tocilizumab (Genetical recombination) Actemra for Intravenous Infusion 80 mg and 400 mg	Chugai Pharmaceutical Co., Ltd.	June 13, 2008
Deferasirox Exjade Dispersible Tablets 125 mg and 500 mg	Novartis Pharma K.K.	June 16, 2008
Adalimumab (Genetical recombination) Humira Subcutaneous Injection 40 mg Syringe 0.8 mL	Abbott Japan Co., Ltd.	June 18, 2008
Irbesartan Avapro Tablets 50 mg and 100 mg	Dainippon Sumitomo Pharma Co., Ltd.	July 1, 2008
Irbesartan Irbetan Tablets 50 mg and 100 mg	Shionogi & Co., Ltd.	July 1, 2008
Famciclovir Famvir Tab. 250 mg	Asahi Kasei Pharma Corporation	July 1, 2008
Raltegravir Potassium Isentress Tablets 400 mg	Banyu Pharmaceutical Co., Ltd.	July 7, 2008
Norethisterone/Ethinylestradiol Lunabell Tablets	Nobelpharma Co., Ltd.	July 8, 2008
Argatroban Hydrate Slonnon HI Injection 10 mg/2 mL[*4]	Daiichi Sankyo Co., Ltd.	July 16, 2008
Argatroban Hydrate Novastan HI inj. 10 mg/2 mL[*4]	Mitsubishi Tanabe Pharma Corporation	July 16, 2008
Sapropterin Hydrochloride Biopten Granules 2.5%[*5]	Asubio Pharma Co., Ltd.	July 16, 2008
Sodium Risedronate Hydrate Actonel Tab. 17.5 mg[*6]	Ajinomoto Co., Inc.	July 16, 2008
Sodium Risedronate Hydrate Benet Tablets 17.5 mg[*6]	Takeda Pharmaceutical Company Limited	July 16, 2008
Diazoxide Aroglycem Capsules 25 mg	Schering-Plough K.K.	July 22, 2008
Yttrium (^{90}Y) Ibritumomab Tiuxetan (Genetical recombination) Zevalin yttrium (^{90}Y) injection	Bayer Yakuhin, Ltd.	August 4, 2008
Indium (^{111}In) Ibritumomab Tiuxetan (Genetical recombination) Zevalin indium (^{111}In) injection	Bayer Yakuhin, Ltd.	August 4, 2008
Levobupivacaine Hydrochloride POPSCAINE 0.75% inj. 75 mg/10 mL, POPSCAINE 0.75% inj. 150 mg/20 mL, POPSCAINE 0.25% inj. 25 mg/10 mL, POPSCAINE 0.25% inj. bag 250 mg/100 mL, POPSCAINE 0.75% inj. syringe 75 mg/10 mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	August 5, 2008
Estradiol Julina 0.5mg	Bayer Yakuhin, Ltd.	September 16, 2008
Mometasone Furoate Hydrate Nasonex Nasal Solution 50 μ g 56 metered spray	Schering-Plough K.K.	September 16, 2008

Cetuximab (Genetical recombination) Erbitux Injection	Merck Serono Co., Ltd.	September 19, 2008
Tazobactam·Piperacillin Hydrate ZOSYN	Taiho Pharmaceutical Co., Ltd.	October 1, 2008
Neostigmine Methylsulfate·Atropine Sulfate Hydrate AtvagoReverse Intravenous Injection Syringe 3 mL and 6 mL	Terumo Corporation	October 1, 2008

*1: An additional indication for "rhinitis allergic"

*2: Additional indications for "rheumatoid arthritis (including prevention for structural damage of joints), polyarticular-course juvenile idiopathic arthritis, and systemic-onset juvenile idiopathic arthritis"

*3: An additional indication for "prophylaxis of vein thromboembolism in patients undergoing abdominal surgery who are at risk for venous thromboembolism"

*4: An additional indication for "prophylaxis of thrombosis in patients with heparin-induced thrombocytopenia (HIT) type II"

*5: An additional indication for "reducing blood phenylalanine levels in patients with hyperphenylalaninemia (tetrahydrobiopterin-responsive hyperphenylalaninemia) due to tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency"

*6: An additional indication for "Paget disease of bone"

Reports on adverse reactions associated with influenza vaccines in FY2007 (Conclusion of the vaccine adverse reaction review committee)

Reports on adverse reactions associated with influenza vaccines since FY2003 have been described in the Pharmaceuticals and Medical Devices Safety Information. This section represents a summary of the reporting status etc. on adverse reactions associated with the influenza vaccines in FY2007. **Table 1** indicates estimated amount of influenza vaccine consumption, number of reported adverse reaction cases, and number of adverse reactions reported in the past 5 years, and **Table 2** for the reporting status of adverse reactions associated with influenza vaccinations in FY2007, according to the number of cases per age group, sex, and outcome. As for reported cases of death and cases with sequelae in FY2007, its summaries and the results of a review by the vaccine adverse reaction review committee consisted of specialists in infectious diseases and viruses are shown in **Tables 3 and 4**, respectively.

In addition, **Table 5** indicates the number of adverse reactions reported from influenza vaccination (reported regardless of causality) in FY2007 in accordance with the Vaccine Adverse Reaction Reporting System for your reference.

Table 1 Estimated amount of influenza vaccine consumption, number of reported adverse reaction cases, and number of adverse reactions reported in the past 5 years

	FY2003	FY2004	FY2005	FY2006	FY2007
Estimated amount of consumption	Approximately 14.63 million vials	Approximately 15.98 million vials	Approximately 19.32 million vials	Approximately 18.77 million vials	Approximately 22.57 million vials
Number of reported adverse reaction cases	162 cases	113 cases	102 cases	107 cases	122 cases
Number of adverse reactions reported	259 events	205 events	139 events	149 events	190 events

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

Age group	Total		Recovered/ Remission		Unrecovered		Unknown		Sequelae		Death	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	122		92		11		10		5 (2)		4 (0)	
	57	65	41	51	4	7	7	3	4 (2)	1 (0)	1 (0)	3 (0)
Under age of 10	33		26		3		2		2 (1)			
	20	13	15	11	1	2	2		2 (1)			
10s	20		16		2		2					
	8	12	5	11	1	1	2					
20s	6		6									
	1	5	1	5								
30s	11		7		2		2					
	2	9	2	5		2		2				
40s	12		9						3 (1)			
	8	4	6	3					2 (1)	1 (0)		
50s	4		3		1							
	2	2	2	1		1						
60s	13		11				2					
	8	5	6	5			2					
70s	14		9		3		1				1 (0)	
	6	8	3	6	2	1	1					1 (0)
80s	6		3								3 (0)	
	2	4	1	2							1 (0)	2 (0)
90s	2		2									
		2		2								
Unknown	1						1					
		1						1				

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

2. Duplicate counting when reported by multiple companies.

Table 3. Death case summary etc.

No.	Case summary	The review result by the study group
1	Male in 80s Adverse reaction: pneumonitis Past history/complications: gastrinoma, insomnia, benign prostatic hyperplasia, Parkinson's disease, bronchopneumonia The patient received influenza HA vaccination. There was no apparent abnormality at the vaccination. 1 day after vaccination, the patient complained of chest distress and vomited. The patient visited the hospital on the same day for persistent chest symptom. Blood pressure decreased and oxygen saturation decreased, and infiltrative shadows in the entire right lung field were confirmed by chest X-ray. The patient was hospitalized based on the diagnosis of pneumonia and respiratory failure. Intratracheal intubation and artificial respiration were started. The patient was diagnosed with serious respiratory failure associated with pneumonia. Antibiotics and methylprednisolone were administrated. 2 days after vaccination, blood pressure decreased and the patient died from acute respiratory failure.	This is a case of which the patient was diagnosed with pneumonia and respiratory failure 1 day after vaccination, which led to death on 2 days after vaccination. As the symptoms developed early and the patient complicated with bronchopneumonia etc., this case cannot be evaluated as having causality with the influenza vaccination.
2	Female in 80s Adverse reaction: hypertension, cerebral haemorrhage Past history/complications: aortic aneurysm, chronic renal failure, hypertension, cardiac failure congestive, hyperuricaemia The patient was referred to the hospital and hospitalized for cardiac failure congestive with valvular disease and hypertension, chronic renal failure, and aortic aneurysm. Afterwards, the symptoms improved by diuretic and change in control of antihypertensive. 9 months after hospitalization, the patient received influenza HA vaccination. On the next year, the patient received influenza HA vaccination. 1 day after vaccination, there was no particular problem. 2 days after vaccination, blood pressure increased and loss of consciousness developed. CT confirmed thalamus haemorrhage and rupture. On the same day, the patient died from cerebral haemorrhage.	This is a case of which hypertension was confirmed 2 days after vaccination and the patient died from cerebral haemorrhage. However, this case cannot be evaluated as having causality with the influenza vaccination as the possible influences of primary diseases and complications were also considered.
3	Female in 80s Adverse reaction: neutropenia, pneumonia, pyrexia, productive cough Past history/complications: hypertension, type 2 diabetes mellitus, chronic renal failure The patient had been visited the hospital once a month for essential hypertension, type 2 diabetes mellitus, and chronic renal failure. Diabetes mellitus was controlled by diet therapy alone. The patient had no allergy. The patient received influenza HA vaccination. There was no physical abnormality to the patient before the vaccination. 1 day after vaccination, pyrexia and productive	This is a case of which the symptoms were confirmed 1 day after vaccination and on 2 days after vaccination, the patient was diagnosed with pneumonia and neutropenia. The symptoms developed early and no abnormality was confirmed at the interview with a physician before the vaccination. However, there is insufficient information, such as lack of detailed information regarding blood test, etc., the causality between the event and the influenza vaccination cannot be evaluated.

	cough developed. Although the patient took OTC cold medicine and OTC antipyretic analgesic, the symptoms did not improve and anorexia intensified. In the evening, face oedema and lower leg oedema developed. 2 days after vaccination, the patient received medical consultation. Lobar pneumonia of right lung, bilateral pleural effusion, and congestion from aggravation of chronic cardiac failure were confirmed by chest X-ray. Neutropenia, macrocytic normochromic anaemia, and aggravation of chronic cardiac failure were confirmed by blood test. In addition, although hypoglycaemia was confirmed, the symptom improved on the same day. Though the patient was administered carperitide (genetical recombination), furosemide, dopamine hydrochloride, lenograstim (genetical recombination), sulbactam sodium/ampicillin sodium, minocycline hydrochloride, she did not respond to the treatment. Oxygen saturation decreased, difficulty in maintenance of blood pressure, and oliguria developed. No improvement was confirmed through chest X-ray, as well. 4 days after vaccination, the patient died from acute respiratory failure and acute pneumonia.	
4	Female in 70s Adverse reaction: death Past history/complications: intestinal obstruction, breast cancer, pulmonary tuberculosis The patient had no apparent adverse reactions associated with influenza HA vaccines in the past two vaccinations (last year and the year before last). Since there was no physical abnormality to the patient before the vaccination, she received influenza HA vaccination. The condition of the patient after the vaccination was unknown. 4 days after vaccination, the patient was found dead in the bathroom.	The patient died 4 days after vaccination. However there is insufficient information on detailed situation from the vaccination to death, the causality between the event and the influenza vaccination cannot be evaluated.

HA: Haemagglutinin

CT: Computed Tomography Scan

Table 4 Sequelae case summary etc.

No.	Case summary	The result of a review by the study group
1	Male under age of 10 Adverse reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: nasopharyngitis The patient received the first influenza HA vaccination. 36 days after the first vaccination, the patient received the second vaccination. 31 days after the second vaccination, cold symptoms occurred. Afterwards, bad mood, irritability, and visual impairment developed, and the patient was hospitalized. 40 days after the second vaccination, the patient was diagnosed with acute disseminated encephalomyelitis based on the result of brain MRI. 43 days after the second vaccination, the symptoms were improved through steroid pulse therapy and intravenous immunoglobulin. 92 days after the second vaccination, the patient was discharged from the hospital. 286 days after the second vaccination, although the symptoms improved, the patient had sequelae of visual acuity reduced and muscular weakness.	The symptoms had been observed since 31 days after the second vaccination. On 40 days after the second vaccination, the patient was diagnosed with acute disseminated encephalomyelitis. The causality with influenza vaccination cannot be denied, as there was no other factors that caused neurological disorder.
2	Male under age of 10 Adverse reaction: acute encephalopathy Past history/complications: none The patient received influenza HA vaccination. 7 days after the first vaccination, the patient received the second vaccination. 5 days after the second vaccination, the patient visited the hospital for pyrexia and received the administration of acetaminophen suppository. On the same day, due to generalised convulsion and loss of consciousness leading to unstable respiratory status, artificial ventilation was implemented. Based on the diagnosis of acute encephalopathy, control of intracranial pressure, steroid pulse therapy, and administration of acyclovir were started. Midazolam was administrated for convulsion. Development of generalised high voltage slow wave was confirmed by electroencephalogram. 13 days after the second vaccination, as respiratory status and level of consciousness improved, artificial ventilation was discontinued. Afterwards, in spite of thyrotropin-releasing hormone therapy and rehabilitation, the patient had serious psychomotor regression. Brain MRI confirmed diffuse cerebral atrophy. 95 days after the second vaccination, the patient became bedridden. Increased antibody titers of human herpesvirus 6 (HHV6) were confirmed. 202 days after the second vaccination, as onset of convulsion was controlled by polypharmacy of antiepileptic drugs, electroencephalogram abnormality persisted. 562 days after the second vaccination, the patient became bedridden due to quadriplegia and was unable to communicate verbally.	This is a case of which the patient was diagnosed with acute encephalopathy after the vaccination. Although it has been long since the patient received the vaccination, due to the fact that increased antibody titers of HHV6 were reported, possible effect of HHV6 infection is also considered. However, the causality with influenza vaccination cannot be evaluated due to lack of detailed information regarding antibody titers at the time of diagnosis etc.

3	Male in 40s Adverse drug reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: none The patient received influenza HA vaccination. 4 days after vaccination, pyrexia and urinary retention developed and the patient was hospitalized. 15 days after vaccination, as urinary retention improved, the patient was discharged from the hospital. 16 days after vaccination, the patient was transported by the ambulance due to consciousness clouding and inarticulateness and was hospitalized. The patient was diagnosed with acute disseminated encephalomyelitis based on disseminated high intensity confirmed by brain MRI and pleocytosis. The treatment was started with steroid pulse therapy and anticonvulsant. 19 days after vaccination, the patient was admitted to the ICU (intensive care unit) due to progress of the condition. 49 days after vaccination, state of consciousness improved through steroid pulse therapy and intravenous immunoglobulin. The patient became able to communicate verbally. Although he had swallowing difficulty, phonation difficulty, and left upper limb paralysis, walking became possible with lower limbs. 87 days after vaccination, although the condition improved, the patient had sequelae of swallowing difficult, dysarthria, and left upper limb paralysis.	Acute disseminated encephalomyelitis has been developed since 16 days after vaccination. The causality with influenza vaccination cannot be denied, as there was no other factor that caused neurological disorder.
4	Male in 40s Adverse drug reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: none The patient received influenza HA vaccination. There was no adverse reaction after the vaccination. 8 days after vaccination, the patient visited the hospital due to queasy and was diagnosed with diarrhoea and vomiting. 10 days after vaccination, the patient had queasy and slight fever. 11 days after vaccination, bilateral chest pain developed. The slight fever persisted. 14 days after vaccination, pollakiuria, pyrexia and white blood cell increased developed. Although ceftriaxone sodium was administrated for possible acute prostatitis, pyrexia developed. The symptoms improved through administration of silodosin for pollakiuria. 20 days after vaccination, giddy feeling and headache occurred. Slight fever persisted. 22 days after vaccination, stumbling, numbness in both hands, shaking of both hands, and urinary retention developed. Gait disturbance became significant. 24 days after vaccination, the patient was hospitalized due to aggravation of gait disturbance. As the patient had ataxic gait, postural tremor of finger, numbness of fingers, changes of perception in cervicothoracic area, cervical vertebrae disorder was suspected. Based on extensive lesion of	Neurological disorders occurred 20 days after vaccination, and on 24 days after vaccination, the patient was diagnosed with acute disseminated encephalomyelitis. Though it might be an infectious disease because of nausea and pyrexia, there is insufficient information. Therefore, the causality between the event and the influenza vaccination cannot be evaluated.

	cerebrospinal fluid and enlargement of spinal marrow confirmed by cervical MRI, cerebrospinal fluid cell count increased and cerebrospinal fluid protein increased observed by cerebrospinal fluid examination, and abnormal signals in bilateral cerebral cortex to the deep white matter detected by brain MRI, the patient was diagnosed with acute disseminated encephalomyelitis. The symptoms improved through methylprednisolone pulse therapy. Urinary retention was improved. 38 days after vaccination, tingling sensation of femoral region and neck pain were subsided through the administration of prednisolone and maobushisaishinto (Kampo medicine). 66 days after vaccination, all the symptoms disappeared excluding numbness of anterior femoral region when bending the neck forward.	
5	Female in 40s Adverse drug reaction: leukoencephalomyelitis (acute disseminated encephalomyelitis) Past history/complications: none The patient received influenza HA vaccination. Approximately 3 hours after vaccination, feels poorly and vomiting developed. 1 day after vaccination, the patient was diagnosed with acute disseminated encephalomyelitis based on the results of MRI and CT and was hospitalized. On the same day, as the patient had significant brain oedema, emergency surgical cerebral decompression, brain hypothermia treatment, high-dose steroid therapy, and immunoglobulin therapy were implemented. The patient was put under artificial respiration. 16 days after vaccination, state of consciousness improved. The patient had quadriparesis. Afterwards, the dose of steroid was tapered while undergoing rehabilitation. 87 days after vaccination, cranioplasty was performed. 116 days after vaccination, the patient was discharged from the hospital. Right limb paresis mildly persisted. Mild memory impairment was suspected.	The symptoms had been observed since approximately 3 hours after vaccination, and the patient was diagnosed with acute disseminated encephalomyelitis 1 day after vaccination. Although other factors cannot be ruled out since onset of the symptoms occurred immediately, the causality between the event and influenza vaccination cannot be evaluated due to lack of detailed information.

MRI: Magnetic Resonance Imaging

Table 5 Reports of adverse reactions by influenza vaccines in FY2007 (reported regardless of causality)

	Total	Recovery	Death	Serious	Hospitaliza-tion	Sequelae	Others	N/A
Total	40	20	2		9		7	2
1 Immediate systemic reaction	2	1					1	
1A Anaphylaxis								
1B Systemic urticaria	2	1					1	
2 Encephalitis, encephalopathy	2	1			1			
3 Convulsion	1	1						
4 Movement disorder								
5 Other nerve disorders	4				3			1
6 Local abnormal swelling (over elbows)								
7 Rash generalized	3	2					1	
8 Pyrexia of 39°C and higher	5	4			1			
9 Other abnormal reactions	2				2			
10 Nonstandard reports	21	11	2		2		5	1
10A Local reaction (redness and swelling etc.)	3	2					1	
10B Systemic reaction (pyrexia etc.)	8	5			1		2	
10C Others	10	4	2		1		2	1

(Note)

1. Listed numbers are provisional figures and are subject to partial change in the future.
2. The Vaccine Adverse Reaction Reporting System is intended based on Immunization Practices for collecting the information of change in health conditions of the vaccinated individuals by the Preventive Vaccination Law, providing the public a broad range of information, where the individuals subject to the system are limited only to the target of routine vaccination.