Pharmaceuticals and Medical Devices Safety Information

No. 262 October 2009

Table of Contents

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

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

Pharmaceuticals and Medical Devices Safety Information

No. 262 October 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

PMDA Medical Safety Information

1. What is PMDA Medical Safety Information?

Information that Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) had begun posting "PMDA Medical Safety Information" on its website was given in Pharmaceuticals and Medical Devices Safety Information No. 241 dated November 29, 2007. PMDA Medical Safety Information provides information regarding similar and repeatedly reported adverse health events or notifications from the regulatory authority for a package insert revision, taken from medical incident reports associated with drugs or medical devices or adverse drug reactions/malfunction reports collected to date, described in a manner that is easy-to-understand and illustrated with photographs and diagrams. PMDA Medical Safety Information includes important reminders regarding the promotion of safe use of drugs and medical devices, and are prepared btaking into account advices of physicians, pharmacists, nurses, clinical engineers, other healthcare professionals, specialists including those in the field of ergonomics, as well as industry organizations including MAHs of drugs and medical devices. The website will be continuously updated with new medical safety information. Safety managers at medical institutions are encouraged to make use of PMDA Medical Safety Information bulletins in promoting the safe use of drugs and medical devices.

2. Currently Available PMDA Medical Safety Information

No	Date of Issue	Title
1	November, 2007	Points to note in case of obstruction of feeding tube 1. Precautions for clearing obstruction of feeding tube-1 2. Precautions for clearing obstruction of feeding tube-2 http://www.pmda.go.jp/english/service/pdf/safety/No1.pdf
2	November, 2007	Recall of Resuscitators 1 Request for cooperation in the voluntary recall of resuscitators 2 Products targeted for recall http://www.pmda.go.jp/english/service/pdf/safety/No2.pdf
3	January, 2008	Precautions against improper connection of speech valves etc. to tracheotomy tubes 1. Precautions for speech valve connection-1 2. Precautions for speech valve connection-2 3. Products at risk of improper connection 4. Products designed to prevent improper connection http://www.pmda.go.jp/english/service/pdf/safety/No3.pdf
4	June, 2008	Precautions against smoking and use of fire in Long-term Oxygen Therapy (LTOT) 1. Precautions for LTOT-1 2. Precautions for LTOT-2 3. Precautions for LTOT-3 http://www.pmda.go.jp/english/service/pdf/safety/No4.pdf
5	June, 2008	Handling of lancing devices for obtaining blood samples 1. Types and handling precautions of lancing devices for obtaining blood samples 2. Precautions for Type 3 lancing devices wherein a component adjacent to a needle is not disposable 3. Other types of lancing devices 4. Other precautions for directions for use

		http://www.pmda.go.jp/english/service/pdf/safety/No5.pdf
6	October, 2008	Precautions against misuse (overdose) of antirheumatic methotrexate preparations 1. How to take antirheumatic methotrexate preparations 2. Precautions for handling antirheumatic methotrexate preparations-1 3. Precautions for handling antirheumatic methotrexate preparations-2 http://www.pmda.go.jp/english/service/pdf/safety/No6.pdf
7	January, 2009	Precautions in Artificial Respiration (No.1) 1. What should be checked when a low-pressure alarm occurs 2. Contraindications for concomitant use with a heat and moisture exchanger and a heated humidifier http://www.pmda.go.jp/english/service/pdf/safety/No7.pdf
8	February, 2009	Compatibility between a "Type A" Needle (JIS T 3226-2) and a Insulin Pen (JIS T 3226-1) 1. Compatibility between a "Type A" needle and a Insulin pen 2. Precautions for the combination of OptiClick and a pen needle http://www.pmda.go.jp/english/service/pdf/safety/No8.pdf
9	February, 2009	Recall for Jackson-Rees Circuits 1. How to find Jackson-Rees circuits with a risk of airway obstruction 2. Recalled Jackson-Rees circuit products http://www.pmda.go.jp/english/service/pdf/safety/No9.pdf
10	May, 2009	Good Management & Maintenance of Automated External Defibrillators (AEDs) 1. Daily Inspection 2. Check and Replacement of Consumables http://www.pmda.go.jp/english/service/pdf/safety/No10.pdf
11	August, 2009	Precautions in Artificial Respiration (No. 2) 1. Precaution when connecting an airway pressure tube 2. Points for handling a heated humidifier http://www.pmda.go.jp/english/service/pdf/safety/No11.pdf
12	September, 2009	Tubing Misconnections in Tourniquets (Hemostatic Cuffs) 1. Precautions for handling tourniquets (hemostatic cuffs) No. 1 2. Precautions for handling tourniquets (hemostatic cuffs) No. 2 3. Request for medical institutions http://www.pmda.go.jp/english/service/pdf/safety/No12.pdf
13	October, 2009	Accidents on Compressed Gas Cylinder Replacement 1. Precautions for handling compressed gas cylinders 2. Measures to prevent tubing misconnections http://www.pmda.go.jp/english/service/pdf/safety/No13.pdf

3. Closing comments

PMDA Medical Safety Information bulletins are available on the pharmaceuticals and medical devices information website (http://www.info.pmda.go.jp/). There is also a "Pharmaceuticals and Medical Devices Information E-mail Alert Service" available. You are encouraged to sign up for this free service at the following URL.

PMDA's "Pharmaceuticals and Medical Devices Information E-mail Alert Service"
http://www.info.pmda.go.jp/info/idx-push.html

2

The Relief System for Sufferers from Adverse Drug Reactions and Diseases Infected from Biological Products

1. Introduction

The Relief System for Sufferers from Adverse Drug Reactions was established in 1980 to bring prompt relief with simple procedure to persons who suffered from adverse health effects such as disorders or disabilities caused by adverse reactions of pharmaceuticals (including over-the-counter drugs), despite proper use of the pharmaceuticals. This is a public service funded by contributions of marketing authorization holders of pharmaceuticals and biological products as part of fulfilling their social responsibilities. As of August 31, 2009, approximately 7,200 people (the actual number of sufferers) have been granted relief benefits.

In 2004, the Relief System for Infections Derived from Biological Products, which is also a public service, was established to bring prompt relief with simple procedure to persons who suffered from adverse health effects including infectious disorders or disabilities caused by biological products, despite proper use of the biological products.

For details of these services, please refer to the PMDA website (http://www.pmda.go.jp/kenkouhigai.html [in Japanese]) (videos available).

Recently, the number of applications to the Relief System for Sufferers (Relief System for Sufferers from Adverse Drug Reactions and Diseases Infected from Biological Products, the same shall apply hereafter) has been increasing (926 claims were submitted to the Relief System for Sufferers in the 2008 fiscal year). In response to criticisms that this relief system is still not well known in public, the procedures for claiming relief benefits (information to be provided to sufferers) and examples of cases applicable for relief benefits are presented here for further use of this service by people who suffer adverse health effects.

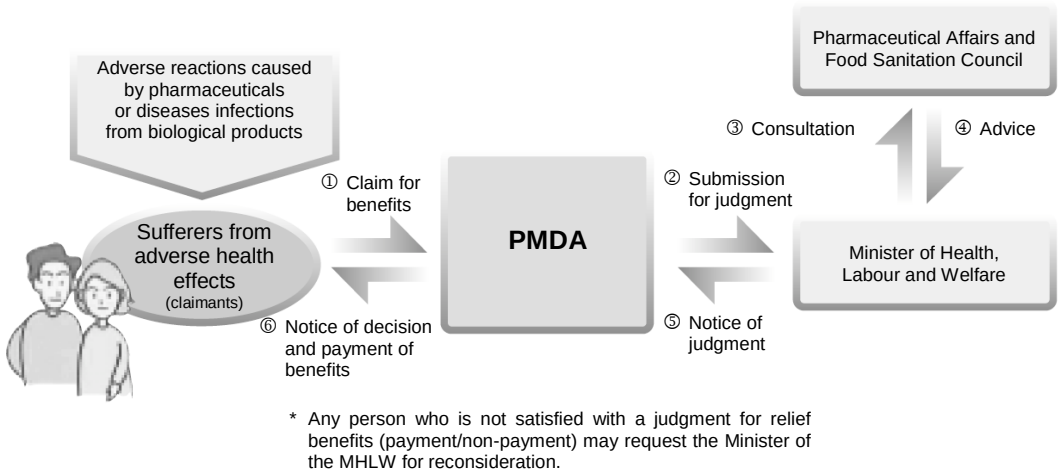
2. Claims for relief benefits (information to be provided to sufferers from adverse health effects)

When healthcare providers in the course of their work counsel patients on disorders or disabilities who are suspected to be suffered from possible adverse health effects caused by pharmaceuticals or biological products, they should provide information regarding this system and the following matters to the patients suffering from the adverse health effects, or to the bereaved family of the sufferers.

(1) How to claim for relief benefits

Claims for relief benefits should be submitted by the patients suffering from adverse health effects caused by an pharmaceutical or biological products, or by his/her bereaved family (hereafter claimants) directly to PMDA.

Flowchart of the relief system



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

(2) Types of benefits and deadlines for claiming

There are seven benefit types: Medical Expenses, Medical Allowances, Disability Pension, Pension for Raising Handicapped Children, Bereaved Family Pension, Lump-sum Benefits for Bereaved Families, and Funeral Expenses (For details of each benefit and deadlines for claiming, refer to **Document 1** on pages 9 to 11).

(3) Documents required for claiming

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

To receive relief benefits, it is necessary to establish the causal relationship between disorder and/or disability and pharmaceuticals.

When claiming for a relief benefit, following documents are required; a) medical certificate written by the physician who treated the adverse health effects caused by adverse reactions or infections, b) proof of prescription, c)or proof of purchase if the over-the counter-drug was purchased from pharmacy or drugstore. Claimants submit to PMDA the above documents written by their physicians and/or pharmacists, together with the claims filled in by the claimants.

All required forms, including claims forms and medical certificate forms, are available from PMDA and can be sent free of charge upon the request of claimants by PMDA. The necessary forms are also available for download at PMDA's websites; http://www.pmda.go.jp/kenkouhigai/fukusayo_dl/ for Relief System for Sufferers from Adverse Drug Reactions, http://www.pmda.go.jp/kenkouhigai/kansen_dl/ for Relief System for Sufferers from Diseases Infected from Biological Products.

(4) Contact office for adverse health effects relief system

The documents required to claim relief benefits include a written request for relief according with the benefit type, a physician's certificate (with diagnosis), a proof of medical examination, and a proof of prescription. When claiming the relief benefits, please contact PMDA Relief System Consultation Service in advance 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. Example cases of relief benefit payments

(1) Cases approved for relief benefits

In this section, specific cases where relief benefits have been approved are presented. .

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

[Relating to Medical Expenses/Medical Allowances]

<Oculomucocutaneous syndrome>

Female in her 50s. Loxoprofen sodium was prescribed to the patient for treatment of pain in the right elbow. When the patient visited hospital again because of persistent pain, she was diagnosed with gout and allopurinol was prescribed. Administration of allopurinol was discontinued after 14 days when the patient developed blood blisters in the mouth, itching of the eyes and vulva, and pyrexia. She visited hospital the next day because of itching of the torso, onset of conjunctival hyperaemia, and increase in amount of eye discharge. Erythema oedematous was observed and the patient was diagnosed with oculomucocutaneous syndrome. The patient was hospitalized and treated for approximately 5 weeks.

<Interstitial pneumonia>

Female in her 60s. The patient with chronic hepatitis C began receiving combination therapy of peginterferon alfa-2a and ribavirin. Approximately 40 days after initiating treatment a fever of around 38°C and coughing developed. Interstitial pneumonia was diagnosed based on imaging examination results. Steroid therapy was initiated. The patient was hospitalized for 18 days for treatment.

[Relating to Disability Pension/Pension for Raising Challenged Children]

<Drug-induced renal impairment>

Female in her 60s. The patient had been taken omeprazole for reflux oesophagitis, and loxoprofen sodium prescribed for right lymphadenopathy, pain, and fever. Creatinine levels gradually increased and emergency dialysis was conducted for drug-induced renal impairment. Renal function did not recover and maintenance dialysis wasstarted.

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

<Anaphylactic shock (anaphylactoid symptoms)>

Female in her 70s. Gulcagon was injected intramuscularly as pretreatment for gastroscopy. Immediately after she kept lidocaine hydrochloride in her mouth one minute after the injection, she fell down from her chair. Unconsciousness, respiratory arrest, and feeble pulse were observed. Vascular access for infusion, cardiac massage, artificial respiration, intravenous injection of epinephrine, and intratracheal intubation were conducted. Though a sinus rhythm was restored she was comatose and transferred to ICU (intensive care unit). She died despite continuous the treatment by artificial respiration and intravenous infusion of vasopressor.

(2) Examples of cases not applicable for relief benefits

Approximately 7,200 people have been approved for relief benefits as of August 31, 2009, while decisions of non-payment of relief benefits have been made for approximately 1,300 people.

The following cases are not applicable under the adverse health effects relief system:

a. Cases of adverse health effects resulting from statutory vaccination (Relief System for Injury to Health with Vaccination is applicable in such cases). However cases of adverse health effects resulting from voluntary vaccinations are applicable for the relief benefits.
b. When it is clear who is resiponsible for adverse health effects, such as in case of product liability of the marketing authorization holder of the pharmaceutical or biological product.
c. Cases where it was necessary to use the pharmaceutical or biological product in an amout exceeding the approved dosage for the purpose of saving the patient's life, even if it was recognized beforehand that such adverse effects may occur

d. Cases where the pharmaceutical or biological product was used for improper use or purpose.
e. Cases of adverse health effects caused by pharmaceuticals not applicable to the relief benefits.
   Pharmaceuticals not applicable to the relief benefits include:
   (1) Pharmaceuticals used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (i.e. anticancer drugs, immunosuppressants, etc.).
   (2) Pharmaceuticals that don't have the possibility to cause sufferings of adverse reactions, such as pharmaceuticals not used directly for the human bodies or pharmaceuticals without pharmacological effects (i.e. insecticides, antimicrobial agents, IVDs, etc.).
f. Cases of mild adverse health effects (including a case where the claimant did not require treatment at admission or outpatient treatment equivalent to admission), or where the deadline of claiming the relief benefit has passed.

Reasons and details of non-applicable cases for the relief benefits in FY2008 are described below (refer to **Document 2** on pages 11 to 12).

As reasons for decision of non-payment, "No causality" accounted for approximately 45%. Payment is not made for the claims where the causal relationship between adverse health effects and pharmaceuticals is not confirmed.

Secondly, approximately 30% of all cases of non-payment were the cases where "Improper purpose or use (Pharmaceuticals or biological products were not used for approved indications or in accordance with appropriate instructions)". Cases where pharmaceuticals or biological products were used in noncompliance with the PRECAUTIONS in the package inserts may not be applicable for the relief benefits under this system whether adverse health effects occurred or not.

The cases where the "Disorder doesn't require patient's admission nor meet the disability criteria" accounted for approximately 20%. Relief benefits are not approved in cases the patient did not require treatment at admission or outpatient treatment equivalent to admission even if causality between the pharmaceuticals and the disorders has been confirmed. Relief benefits are also not approved in cases where disabilities caused by pharmaceuticals fails to meet disability criteria defined under the system, if causality between the disabilities and the pharmaceuticals has been confirmed.

4. Closing comments

Understanding and cooperation of physicians, pharmacists and other healthcare professionals is essential to provide the relief benefits to sufferers from adverse health effects under the adverse health effects relief system.

Adverse reactions can be an unpreventable consequence of pharmaceutical administration, even if pharmaceuticals are used according to instructions with all possible care. Therefore, the relief for sufferers of adverse health effects should be achieved by this system for prompt and uncomplicated relief benefits, apart from civil responsibility. Some healthcare professionals are unwilling to provide diagnosis certificates and/or other documents required in claiming for relief benefits, as they misunderstand such documents as an admittance of their inappropriate medical practice that may have caused the adverse health effects. This system aims to provide prompt relief benefits to people suffering adverse health effects caused by pharmaceuticals in all respects. The certificates and/or other proofs prepared by healthcare professionals are the useful reference materials and play an important role in the decision making process regarding these relief benefits.

As mentioned in the section 2, when adverse reactions occur, or when healthcare professionals are asked on consultation with their patient about the adverse reactions that are possibly applicable for these relief benefits, the healthcare professional should provide information regarding this service to the patient. PMDA hopes for your particular corporation in preparing the documents required to claim these relief benefits in the future.

Document 1. Details of benefits and due for claim, etc. of the Relief System for Sufferers

In cases of disorder (requiring admission)

Medical Expenses

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

The coverage of Medical Expenses includes treatments for disorders requiring admission, which is caused by the adverse reactions of pharmaceuticals, etc., and those similar extents of treatments are required. The disorders requiring admission are not limited to the cases where the patients were actually admitted to hospitals. Patients treated at their home because of certain reasons can also be applicable for Medical Expenses, if the disorders are considered as having similar degree of disorders requiring admission.

[Due for claim] Within 2 years since the payment of costs applicable for Medical Expense Benefit (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 disorder caused by adverse reactios, etc.

Medical Allowances

Benefits are provided for costs other than medical costs (round-trip transportation expenses to hospital, miscellaneous expenses accompanying admission, etc.) for treatment of disorder caused by adverse reactions of pharmaceuticals, etc. The coverage of Medical Expenses includes the treatments for disorders requiring admission, 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)	
A case with 3 days and more of outpatient treatments a month	35,800 yen (monthly amount)
A case with less than 3 days of outpatient treatments a month	33,800 yen (monthly amount)
(In cases with admission only)	
A case with 8 days and more of outpatient treatments a month	35,800 yen (monthly amount)
A case with less than 8 days of outpatient treatments a month	33,800 yen (monthly amount)
(In cases with admission and outpatient treatments)	35,800 yen (monthly amount)

[Due for claim] Within 2 years since the first day of the next month of the month when the treatment may be covered by the Medical Allowance was made (however, for the treatment that was given on and after May 1, 2008, due for claim is within 5 years)

[Claimant] The person who received treatment for disorders caused by adverse reaction, etc.

In cases of a certain degree of disability (causing significant activity limitation in daily life in minimum)

Disability Pension

Benefits are provided to compensate for living costs, etc. of patients aged 18 and older, who suffer from certain degree of disabilities caused by adverse reactions of pharmaceuticals, etc.

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

(1) Grade 1: A degree of disability that prevents a person from performing daily life activities by himself/herself
(In extent that the patient needs full assistance in daily life)

(2) Grade 2: A degree of disability that limits daily life activities of the person significantly or requires significant limitation in his/her daily life performance
(In extent that the the patient do not always need assistance, but his/her daily life performance is limited significantly)

Amount of payment as of April 1, 2009 is as follows:

(1) Grade 1: Annual amount of 2,720,400 yen (monthly amount of 226,700 yen)
(2) Grade 2: Annual amount of 2,175,600 yen (monthly amount of 181,300 yen)

[Due for claim] Deadline for a claim is not specified.
[Claimant] The person with disability caused by adverse reaction, etc. (aged 18 or older)

Pension for Raising Handicapped Children

Benefits are 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.

A person who is responsible for raising a handicapped child refers to a person who is socially accepted as raising the handicapped child by comprehensively considering whether the person have the custody of the child, lives with the children, and suppors the livelihood of the child. The degrees of disabilities are the same as those of Disability Pension.

Amount of payment as of April 1, 2009 is as follows:

(1) Grade 1: Annual amount of 850,800 yen (monthly amount of 70,900 yen)
(2) Grade 2: Annual amount of 680,400 yen (monthly amount of 56,700 yen)

[Due for claim] Deadline for a claim is not specified.
[Claimant] The person who is responsible for raising a child under age of 18 with disability caused by adverse reaction, etc.

In cases of death

Bereaved Family Pension

Benefits are provided for bereaved families in rebuilding their life following the deaths of their main providers 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, 2009 is 2,378,400 yen per year (198,200 yen per month).

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

Lump-sum Allowances for Bereaved Family

Benefits are provided for bereaved families for condolence and sympathy following the deaths from adverse reactions of pharmaceuticals, etc. of their family member who is not the main provider.

For Lump-sum Benefits for Bereaved Family, the equivalence of amount for 36 months of Bereaved Family Pension is paid. Amount of payment as of April 1, 2009 is 7,135,200 yen.

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

Funeral Expenses

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

Amount of payment as of April 1, 2009 is 199,000 yen.

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

Document 2. Reasons and details for ineligibility for the relief benefits, etc.

This section describes the reasons for (decision of) non-payment for the relief benefits under the Relief System for Adverse Drug Reactions.

The proportion of non-payment decision accounted for approximately 15% of all claims in FY2008. (The total number of payment and non-payment was 919 claims. Out of them, no payment decisions were made against 136 claims.).

The reasons for non-payment (FY2008) were "No causality" (45.6%), "Improper purpose or improper use" (28.7%), "The cases where the "Disorder doesn't require patient's admission nor meet the disability criteria" (18.4%), "Impossible to judge" (6.6%), and "Pharmaceuticals inapplicable to the relief benefits" (0.7%).

No causality

"No causality" refers to cases in which the disorders or disabilities are not likely to be caused by adverse reactions of pharmaceuticals.

Improper purpose or improper use

"Improper purpose or improper use" basically includes, in use of the pharmaceuticals that caused adverse health effects, cases where the pharmaceuticals were used in ways other than those approved by the Minister of the MHLW, or cases where the pharmaceuticals were used not in accordance with the PRECAUTIONS in the package inserts.

The following cases are considered as improper use and are not appricable for relief benefits if injuries to health may occur.

- In cases where necessary tests are not conducted without proper justification despite the package inserts include such PRECAUTIONS that "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 cases where the OTC drugs such as common cold drugs or antipyretics and analgesics are concomitantly used with the other pharmaceuticals, although such use is prohibited in the package inserts.

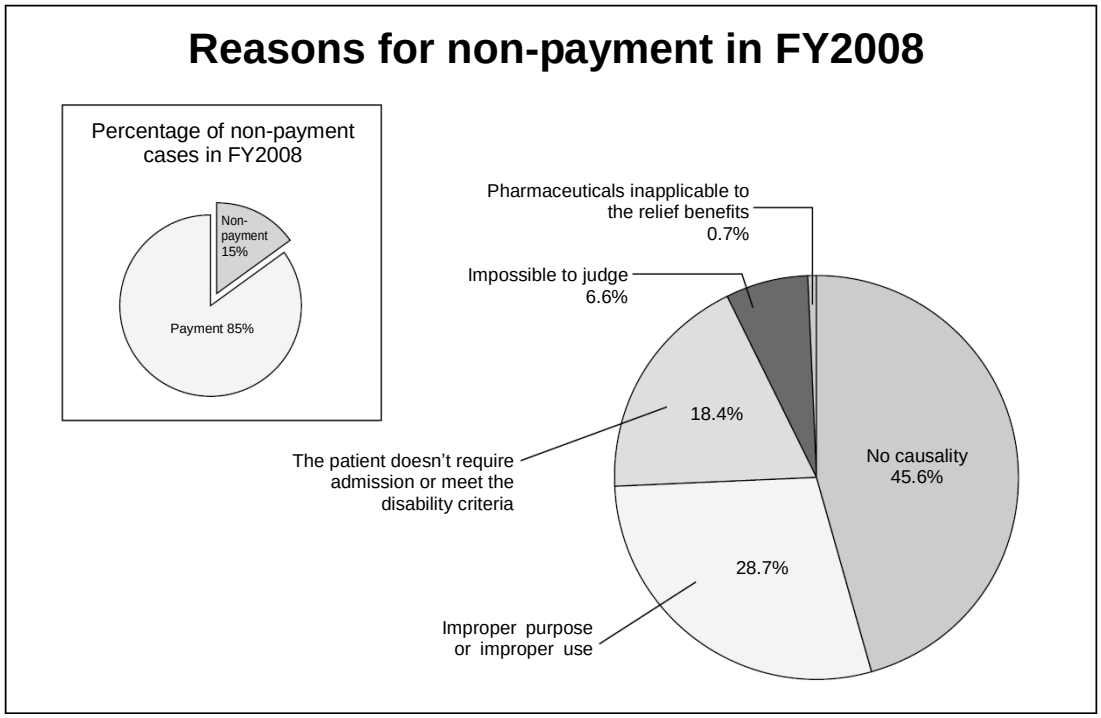
"PRECAUTIONS" originally include necessary information in order to ensure safety of patients who pharmaceuticals are applied to for the purpose of proper use. However, please bear in mind that the Relief System for Sufferers may not be applied to the cases that pharmaceuticals are not used in accordance with the PRECAUTIONS in the package inserts, if injuries to health may occur.

In addition, cases where adverse reactions occur when patients take the pharmaceuticals which have been left without used (so called "unused drug") by self-judgment without instruction of physicians are generally not applicable for the relief benefits by considering such cases as improper use.

The cases where the "Disorder doesn't require patient's admission nor meet the disability criteria"The cases where the "Disorder doesn't require patient's admission nor meet the disability criteria" refers to the cases in which although the causality between pharmaceuticals and the disease is confirmed, the patient didn't require admission or outpatient treatment equivalent to admission to treat the disorders, or didn't meet the criteria of "Disability that prevent a person from performing daily life activities by himself/herself (Grade 1)" or "Disability that requires significant limitation in his/her daily life performance (Grade 2)" for the degree of the

disability.

Generally, the cases with outpatient treatments alone are not applicable for the relief benefits.



Impossible to judge

"Impossible to judge" refers to the cases where it cannot be judged based on the submitted documents whether there are causalities or whether drugs are used for approved indications or in accordance with the instructions.

Pharmaceuticals not applicable to the relief benefits

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

3

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 October 1, 2009)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
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
Dutasteride Avolve Capsules 0.5mg	GlaxoSmithKline K.K.	September 4,2009
Mirtazapine REFLEX TABLETS 15mg	Meiji Seika Kaisha, LTD.	September 7,2009
Mirtazapine REMERON Tablets 15mg	Schering-Plough K.K.	September 7,2009
Pemetrexed Sodium Hydrate Alimta Injection[*8]	Eli Lilly Japan K.K.	September 24,2009
Aliskiren Fumarate Rasilez Tablets 150mg	Novartis Pharma K.K.	October 1,2009

*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 “treatment of patients with rheumatoid arthritis which is not adequately responsive to conventional therapies (including prevention for structural damage of joints)”

*10: An additional indication for **"**treatment of patients with polyarticular-course juvenile idiopathic arthritis (only for cases which are not adequately responsive to conventional therapies)"

*11: An additional indication for "treatment of patients with the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders or polycystic ovarian syndrome"