Pharmaceuticals and Medical Devices Safety Information

No. 206 October 2004

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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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No. 206 October 2004

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

[Outline of Information]

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2	**Reports on Iressa Tablets 250 prospective study (special investigation)**	*P*	Gefitinib is an anticancer drug with the indication for "inoperable or recurrent non-small cell lung cancer" and was first approved in Japan on July 5, 2002 prior to launch overseas. MHLW has been alerted healthcare providers about "interstitial pneumonia" caused by gefitinib under the section "Clinically significant adverse reactions" of the package insert. Lung disorders including interstitial pneumonia have been reported to Ministry of Health, Labour and Welfare since the initial marketing on July 16, 2002. On October 15, 2002, MHLW distributed "Dear Healthcare Professional Letters" regarding acute lung disorders and interstitial pneumonia to the healthcare professionals for cautions. In addition,"Gefitinib Safety Issues Conference" consisting of medical/pharmaceutical expert working group was held on December 25, 2002 and the following additional measures for proper use were taken. The result of a prospective study based on the instruction has been summarized and presented.	9
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1

Safety measures for shock etc. due to injectable antibiotics etc.

(1) Background

It is well recognized that injectable antibiotics and synthetic antibacterials may cause shock/anaphylactoid symptoms in a rare case. As a safety measure,: "① Sufficiently obtain patient's medical history etc. on ahead as shock may occur. Moreover, it is desirable to conduct a skin test beforehand. ② Emergency measures should be prepared in case of shock. Patients should be kept rested throughout administration and carefully monitored." is described in "Important Precautions" of the package insert. In general, intracutaneous testing prior to the use of injectable antibiotics has been implemented in accordance with it.

The Japanese Society of Chemotherapy conducted review for the usefulness of intracutaneous tests and presented a proposal regarding the discontinuation of the intracutaneous tests and the alternative safety measures against shock etc. Additionally, the written request for discontinuation of the intracutaneous tests has been submitted by the Japan Antibiotics Research Association as well. In response to this, the expert working group of the Pharmaceutical Affairs and Food Sanitation Council made a consideration. The conclusion of the consideration as well as request for proper use of injectable antibiotics etc. is presented hereafter.

(2) The proposal by the Japanese Society of Chemotherapy and the written request by the Japan Antibiotics Research Association

1) Summary of the proposal organized by the Japanese Society of Chemotherapy[1)]

- Although there is the description: "it is desirable to conduct a skin test beforehand" in the package insert of β-lactam injectable antibiotics in Japan, significance of intracutaneous testing has not been sufficiently considered.
- There is no evidence supporting the usefulness of intracutaneous testing conducted as a predictor for anaphylactic shock at the time of IV administration of antibacterials.
- The incidents of anaphylactic shock due to β-lactam antibiotics in the US, where intracutaneous testing is not usually implemented, is less frequent compared to Japan. Therefore, it is not likely that intracutaneous testing predicts anaphylactic shock.
- The rate of positive results in intracutaneous testing is predominantly higher than that of the true allergy at medical institutions conducting intracutaneous testing, hence, it is anticipated that there are patients suffering the detriment of not being able to receive necessary antibiotics as treatment.

The Japanese Society of Chemotherapy proposes to discontinue intracutaneous testing of injectable antibacterials as a predictor of anaphylactic shock as soon as possible with regard to these concerns mentioned above and the opinion poll of physicians at medical institutions.

It is necessary to always obtain an allergic history including shock due to antibiotics prior to the administration and to prepare measures against shock during 20 to 30 minutes after initiation of IV administration as anaphylactic shock occurs although extremely infrequent.

2) Summary of written request by the Japan Antibiotics Research Association

- The intracutaneous test for injectable β-lactam is designed to predict allergic reactions due to impurities in the injectable preparation. However, purity of preparations today is greatly improved, consequently, the usefulness of conducting the intracutaneous test may be diminished.
- "Penicillin shock" as a social concern has already been settled and the meaningfulness of continuation of intracutaneous testing is considered to be diminished. Also, products caused frequent penicillin shocks have been identified and the manufacturing has already been discontinued.
- As dose-response of the intracutaneous test has not yet been established, it challenges the current medical ethics.
- The manufacturing lot of the active ingredient in vial for intracutaneous test is different from that for treatment. Furthermore, they frequently do not contain the same additives that are contained in the products.

For the aforementioned reasons, it is concluded that there is no significance in continuation of intracutaneous testing for injectable β-lactam since the test lacks a current scientific evidence.

(3) Summary of the consideration by the expert working group of the Pharmaceutical Affairs and Food Sanitation Council

The expert working group has come to the following conclusion by reviewing the descriptions in the labeling or package insert for injectable antibiotics etc. overseas and in Japan, and current status of adverse reaction reports of shock etc. as well as the proposal by the Japanese Society of Chemotherapy and the written request by the Japan Antibiotics Research Association.

① The significance of conducting intracutaneous tests is minute for the following reasons: intracutaneous testing is not capable of predicting shock/anaphylactoid symptoms. There are disadvantages by conducting intracutaneous tests as there are overwhelmingly more patients with false positives who are missing the opportunity to receive an appropriate treatment than patients with a true allergy and there is a possibility that the allergen may be triggered by conducting intracutaneous tests.

② As a safety measure, it is more important to obtain a sufficient medical history etc. by conducting the medical examination as well as finding shock etc. at an early point and take immediate measures rather than relying on the skin reactions including intracutaneous testing.
Note that it is necessary to provide sufficient information that the reason implementation of skin tests will not be recommended is not because there is no longer shocks due to injectable antibiotics and it has become safe but because the significance of conducting skin tests as a predictor for shock etc. is minute.

③ In principle, patients with a history of allergy should not be administered this product. However, it is considered that this product can be administered after a prior skin test in cases where alternative agents cannot be used for treatment. This is not to deny the usefulness of skin tests for aforementioned cases. However, handling of theses cases is rather unusual and it is considered not suitable to be included in the description of the package insert. Rather, it is more appropriate to widely disseminate information to the medical and pharmaceutical providers by creating guidelines including the actual procedure of the skin test by the Japanese Society of Chemotherapy.

(4) Safety measures based on the consideration by an expert working group of the Pharmaceutical Affairs and Food Sanitation Council

The following safety measures are taken with regard to the aforementioned consideration.

1) Revision of "PRECAUTIONS" in the package insert

Descriptions in "Important Precautions" will be revised as follows.

Since there is no certain method of predicting the onset of shock or anaphylactoid symptoms caused by this drug following measures should be taken:

① Sufficiently obtain patients' medical history etc. in advance. In addition, the patient's allergic histories with antibiotics etc. should be strictly confirmed.

② Emergency measures against shock etc. should be prepared prior to administration.
③ Patients should be kept rested throughout administration and closely monitored. In particular, the patients should be carefully monitored immediately after the start of administration.

2) Provision on information regarding proper use of the product

① Posting in the Pharmaceuticals and Medical Devices Safety Information
MHLW will post an article in this report to broadly inform medical and pharmaceutical providers the background, assessment, and measures regarding this revision.

② Establishment of the guideline for anaphylaxis related to administration of antibacterials
MHLW had requested the Japan Society of Chemotherapy to prepare guidelines on proper use such as the preventative measures for anaphylaxis related to administration of antibiotics etc. and post-event measures etc. and "the Guidelines of Measures for Anaphylaxis Related to Administration of Antibacterials (2004)" was established. This guideline is posted on the Japan Society of Chemotherapy website (http://www.chemotherapy.or.jp/, in Japanese) to widely disseminate not only the society members but also medical and pharmaceutical providers.

1. Introduction
2. Important precautions on administration of IV antibacterials
3. Measures to be taken for the prevention of anaphylactic shocks
4. Monitoring during administration
5. Handling of emergencies
6. Skin reaction test for antibacterials
7. Closing comment

③ Distribution of the leaflet regarding measures against anaphylaxis related to administration of antibacterials etc.
Thorough dissemination of the information on proper use of the products has been facilitated by distribution of the leaflet, "A Guideline for Measures Against Anaphylaxis Related to Administration of Antibiotics (outline of 2004 edition)," (Refer to **Table 1**) that summarizes the outline of the aforementioned guidelines to all the medical institutions by the Federation of Pharmaceutical Manufactures' Associations of Japan (FPMAJ) and by having the MRs of each pharmaceutical company visit medical and pharmaceutical providers.

3) Reports on the number of incidents of shock/anaphylactoid symptoms

To investigate the change in the incidence of shock/anaphylactoid symptoms associated with the withdrawal of the recommendation to conduct general skin reaction tests for injectable antibiotics etc., each company is requested to report the number of incidents of the adverse reactions concerned for the immediate 3 years.

(5) Closing comments

MHLW requests all the medical and pharmaceutical providers to follow the package insert and the guidelines established by the Japan Society of Chemotherapy and to exercise caution against the safety measures for shock etc. due to injectable antibiotics etc. In addition, if you obtain information on adverse reactions associated with such a product, please report to the Safety Division of the Pharmaceutical and Medical Safety Bureau within Ministry of Health, Labour and Welfare in accordance with Article 77, 4-2-2 of the Pharmaceutical Affairs Law.

Table 1

A Guideline for Measures Against Anaphylaxis Related to Administration of Antibiotics (outline of 2004 edition)

1. Important precautions on administration of IV antibacterials

Since there is no certain method of predicting the onset of shock or anaphylactoid symptoms caused by antibiotics, following measures should be taken:

1) Sufficiently obtain patient's medical history etc. in advance. In addition, the patient's allergic histories with antibiotics etc. should be strictly confirmed.
2) Emergency measures against shock etc. must be prepared prior to administration.
3) Patients should be kept rested throughout administration and carefully monitored. In particular, patients should be carefully monitored immediately after the start of administration.

2. Measures to be taken for the prevention of anaphylactic shocks

1) Sufficiently obtain patients' medication and allergic histories in advance.
2) In case of patients with an allergy history related to antibacterials
   ① The patients with a medical history of shock due to antibacterials should be treated as follows:
      i) Administration of such product is contraindicated.
      ii) Administration of similar antibiotics is essentially contraindicated. However, careful administration of another β-lactam which is classified in a different subgroup from such product, is permissible with a confirmed negative skin reaction test. However, be aware of an increased risk of anaphylaxia when administrating.
   ② Assessment for the patients with a medical history of hyper reaction to antibiotics other than shock
      i) Administration of such product is essentially contraindicated. However, careful administration is permissible with a confirmed negative skin reaction test. However, be aware of risk of anaphylaxia when administrating.
      ii) As for similar antibacterials, administration should be conducted with care.
   ③ Skin reaction test for cases of ①- ii) and ②- i) should be initiated with a prick test using an injection product to administer. Also, it is desirable to consult an allergy specialist in advance.

3. Monitoring during administration

1) Administration method:
   ① Patients should be carefully monitored after initiation of administration.
   ② If any of the following symptoms are observed, administration should be discontinued immediately and appropriate measures should be taken.

Symptoms suspected of immediate type hypersensitivity

① Injection site reaction: skin red, welts, pain, itching from the injection site to the nerve center
② Systemic reaction: numbness, feeling hot, headache, vertigo, tinnitus, anxiety, tachycardia, blood pressure decreased, discomfort, oral cavity/throat dysaesthesia, thirst, cough, wheezing, abdominal peristalsis, sweaty, chills, rash

4. Drugs required for the onset of shock etc. (adults and children)

1) Epinephrine (Bosmin®) → anaphylaxis initial treatment
2) Hydrocortisone (Solu-cortef®, etc.) → adrenocorticoids
3) Chlorpheniramine maleate (Polaramine Injection®) → antihistamine
4) Aminophylline (Neophyllin®) → bronchodilator
5) Dopamine (Inovan®, etc.) → vasopressor
6) Infusion solution (physiological saline or lactated Ringer's solution)

5. Symptoms and severity of shock

1) If shock or anaphylactoid symptoms are observed, appropriate measures depending on its symptom should be taken.

	Blood pressure decreased	Consciousness disturbed	Symptoms of airways obstruction	Severity of the symptom
Mild	(–)	(–)	(–)	Mild
Moderate	(+)	(–)	(±)	Moderate
Severe	(+)	(+)	(+)	Severe

2) If moderate to severe shock or anaphylactoid symptoms occur at the medical institution where sufficient respiratory management is not available, the patient should be immediately transferred to another institutions which could cope with such symptoms.

6. Examples of emergency treatment

1) Immediately discontinue IV administration of this antibiotics if any abnormal subjective and objective symptoms are observed.
2) Vital signs, symptoms, and severity should be checked.
3) Mild cases
   ① Administration of infusion: Ensure IV access and prepare for use of required medication.
   ② Administration of oxygen: Conduct as required.
   ③ Symptomatic treatment: Conduct as required.
      a. Chlorpheniramine maleate (Polaramine Injection®)
      b. Hydrocortisone succinate (Solu-cortef®)
   ④ Subcutaneous injection of epinephrine 0.1% (Bosmin®) 0.2–0.5 mg: Administer if there is no improvement in the symptoms.
4) Moderate-severe cases
   ① Administration of epinephrine:
      (Adults) Subcutaneous injection or intramuscular injection of epinephrine 0.1% (Bosmin®) 0.2–1.0 mg.
      Or slow IV administration of 10-fold dilution of epinephrine 0.1% (Bosmin®) 0.25 mg.
      Additional administration should be made every 5–15 minutes if the efficacy is insufficient.
      (Children) Subcutaneous injection of epinephrine 0.1% (Bosmin®) 0.01 mg/kg (max. 0.3 mg).
      Or slow IV administration of 10-fold dilution of epinephrine 0.1% (Bosmin®) 0.01 mg/kg.
      Additional administration should be made every 5–15 minutes if the efficacy is insufficient.
   ② Administration of infusion: Lactated Ringer's solution etc. initiated at approximately 20 mL/kg/h.
      * Appropriately reduce the dosage for elderly patients or patients with cardiac failure or renal failure.
   ③ Administration of oxygen and ensuring an open airway:
      a. Administration of high-concentration (≥60 %) oxygen.
      b. Implement intratracheal intubation and switch to artificial respiration with 100% oxygen. Thyrocricotomy should be conducted if there is significant pharyngeal oedema and intratracheal intubation is not possible.
   ④ Circulation control: The following measures should be taken as required.
      a. Vasopressor administration: Concomitantly administer dopamine 5–20 μg/kg/min., if blood pressure decreased persists.
   ⑤ Administration of corticosteroids
      (Adults) Hydrocortisone succinate (Solu-cortef®) 500–1000 mg IV drip infusion
      (Children) Hydrocortisone succinate (Solu-cortef®) 100–200 mg IV drip infusion

∗ IV administration every 4–6 hours.

⑥ Antihistamine

(Adults)	Chlorpheniramine maleate (Polaramine Injection®)	5 mg IV
(Children)	Chlorpheniramine maleate (Polaramine Injection®)	2.5–5 mg IV

(September 2004, the Review working group on the Intracutaneous Test, the Clinical Study board, the Japan Society of Chemotherapy)

<Reference>

1) The Review working group on the Intracutaneous Test of the Clinical Study board, the Japan Society of Chemotherapy, 51 (8): 492-506 (2003) (In Japanese)

2

Reports on Iressa Tablets 250 prospective study (special investigation)

(1) Introduction

Gefitinib is an anticancer agent with the indication for "inoperable or recurrent non-small cell lung cancer" and was first approved in Japan on July 5, 2002 prior to launch overseas.

MHLW has been alerted healthcare providers about "interstitial pneumonia" caused by gefitinib under the section "Clinically significant adverse reactions" of the package insert. Lung disorders including interstitial pneumonia have been reported to Ministry of Health, Labour and Welfare since the initial marketing on July 16, 2002. As these reported cases developed early after the initiation of administration and the symptoms made rapid progress. On October 15, 2002, MHLW requested relevant companies to revise "PRECAUTIONS" of the package inserts to include interstitial pneumonia in "Warning" section and distributed "Dear Healthcare Professional Letters" regarding acute lung disorder and interstitial pneumonia, to the healthcare providers for cautions. Although the number of reported adverse drug reaction etc. has been decreased since distribution of "Dear Healthcare Professional Letters", acute lung disorder/interstitial pneumonia has been still reported. Therefore, "Gefitinib Safety Issues Conference" consisting of medical/pharmaceutical expert working group was held on December 25, 2002 and the following additional measures for proper use were taken.

① Prior to initiation of treatment with this product, physicians should adequately advise the patients of efficacy and safety of this product, initial symptoms of adverse reaction such as shortness of breath, treatment procedure for non-small cell lung cancer, and the possibility of fatal cases and obtain informed consent.

Companies should thoroughly provide the information on proper use regarding efficacy and safety, etc. to medical institutions.

Healthcare providers should cooperate for the collection of information regarding adverse reactions by the companies.

② This drug should also be administered by doctors with sufficient experience in lung cancer chemotherapy and at medical institutions capable of carrying out sufficient measures in case of emergencies at time of administration.

As there are relative more cases of interstitial pneumonia onset during earlier stage of the drug's administration which have resulted in fatal cases, patients should be carefully monitored for the onset of such serious adverse reactions through hospitalization or under similar conditions of control for at least 4 weeks from the start of administration.

③ This product should be administered with care to patients with acute lung disorders, interstitial pneumonia, or pulmonary fibrosis or patients with a medical history of such diseases, as there are cases of aggravated interstitial pneumonia resulting in death.

④ "Information Materials for Patients" of this drug should be appropriately formulated to cope with the onset of interstitial lung diseases promptly, and specifically include the numbers of adverse reactions and fatal cases to directly alert the patient/family for consultation.

⑤ Immediately conduct experimental research such as a scientific investigation for interstitial pneumonia etc. which is a condition for approval, as well as establishing a review conference etc. consisting of an expert working group to determine the cause and successively report the results.

Reconsider the procedure for collection of information on serious adverse reactions and for information provision for medical institutions etc. in the pharmaceutical company, as well as conducting prospective study/analysis etc. to determine the risk factors for the causation of acute

lung disorders/interstitial pneumonia and the backgrounds etc. of patients at a high risk to facilitate proper use of this product.

The result of a prospective study regarding the measure ⑤ has been recently summarized and presented.

(2) The result of Iressa Tablets 250 prospective study

1) The summary etc. of the prospective study (special investigation)

a) Objectives

The incidence of adverse reactions associated with Gefitinib and its risk factors (causal risk factor, prognosis factor) should be determined as soon as possible.

① Investigate the causal risk factors and patient background for treatment-related acute lung disorders/interstitial pneumonia in the cases of Japanese patients with refractory non-small cell lung cancer treated with Iressa.

② Investigate the incidence of treatment-related acute lung disorders/interstitial pneumonia in the cases of Japanese patients with refractory non-small cell lung cancer treated with Iressa.

③ Investigate the incidence of skin disorders (including photosensitivity), liver disorder, and gastrointestinal disorders such as diarrhoea etc.

b) Patients

Patients with inoperable or recurrent non-small cell lung cancer and cases in which this product is used for the first time

c) Follow-up period

8 weeks after the start of administration of this product

d) Investigation procedure

Central registration system

e) Investigation period and number of patients

① Investigation period: June 2003 – March 2004

② Registration period: June 2003 – December 2003

③ Number of target cases: 3000 cases

2) The result of the prospective study (special investigation)

a) Outline

① Number of institutions: 698 (841 departments)

② Number of cases: 5147 cases

③ Number of registered cases: 3354 cases

④ Number of collected case cards: 3350 cases

⑤ Number of evaluable cases for safety: 3322 cases

⑥ Number of evaluable cases for efficacy: 3243 cases

b) Safety

① Adverse reactions

Adverse reactions were observed in 1867 cases (3194 reports) out of 3322 evaluable cases for safety. The incidence of adverse reactions was 56.2%.

Major adverse reactions were 568 of rash (17.1%), 369 of hepatic function abnormal (11.1%), and 367 of diarrhoea (11.1%). Incidence of adverse reactions other than above was less than 5.0%. As for photosensitivity, although there were no reports in this investigation, 3 cases have been reported prior to the investigation.

② Serious adverse events

462 cases (622 reports) were serious amongst adverse events that were undesirable, unintended signs, symptoms, or diseases occurred during/after administration of this product regardless of causality in 3322 evaluable cases for safety. The incidence of serious adverse events was 13.9%.

Major serious adverse events were 149 of interstitial pneumonia (4.5%), 55 of pneumonia (1.7%), 37 of lung disorder (1.1%), 34 of hepatic function abnormal (1.0%), 13 of diarrhoea (0.4%), 11 of

renal function disorder (0.3%), and liver disorder 10 (0.3%). The incidence of adverse events other than above was less than 0.3%.

③ Acute lung disorder/interstitial pneumonia

The incidence of acute lung disorders/interstitial pneumonia in 3322 evaluable cases for safety was 6.5% (215/3322 cases) [95% confidence interval (hereinafter called CI): 5.7%–7.4%] by primary physicians' assessment. The incidence of acute lung disorders/interstitial pneumonia was 5.8% (193/3322 cases) based on the comprehensive assessment using each individual case record and X-ray and CT images by the judging committee. Furthermore, based on the assessment by the judging committee, mortality rate was 38.9% (75/193 cases) among all the cases with adverse reactions and 2.3% (75/3322 cases) among the evaluable cases for safety.

3) Discussion on acute lung disorders/interstitial pneumonia

The diagnosis for acute lung disorders/interstitial pneumonia is not always easy since there are cases that include various other diseases and disorders. The judging committee consisting of expert working group of radiologist, clinical oncologist, and respiratory specialist has reviewed 140 cases of which images were obtained among reported cases of acute lung disorders/interstitial pneumonia by the primary physicians in this investigation.

a) Incidence

The incidence of acute lung disorders/interstitial pneumonia judged by primary physicians was 6.5% (215/3322 cases) in this investigation. As the judging committee refuted the diagnosis as acute lung disorder/interstitial pneumonia for 22 cases out of 215 cases, the incidence of acute lung disorders/interstitial pneumonia exclusive of these 22 cases was 5.8% (193/3322 cases). There is no substantial difference between these figures and the figures reported in the past investigations (1.6%–11.8%).

b) Causal factors

According to the result of multivariate analysis, the increased incidence was suggested to be as follows : cases of ≥ PS2 [≥ PS2 cases: ≤ PS1 cases; estimated hazard ratio (hereinafter called HR) = 2.15, 95% CI: 1.44–3.21, $p < .001$], cases with a history of smoking [cases with a smoking history : cases without a smoking history; HR = 1.99, 95% CI: 1.25–3.16, $p = .004$], cases complicated with interstitial pneumonia at the time of initial administration of this product [cases with a complicated interstitial pneumonia : cases without a complicated interstitial pneumonia; HR = 2.50, 95% CI: 1.18–5.28, $p = .016$], and cases with a history of chemotherapy [cases with a history of chemotherapy : cases without a previous history of chemotherapy: HR = 1.79, 95% CI: 1.05–3.04, $p = .032$]. The factor regarding a history of chemotherapy was suggested as a causal factor for the first time in this investigation among the other factors previously reported in the past investigations.

c) Factors for poor prognosis (fatal case)

Regarding factors for poor prognosis (fatal case), the higher mortality rate was suggested to be as follows; male patients [male: female; HR = 0.27, 95% CI: 0.11–0.69, $p = .006$] and cases of ≥ PS2 [≥ PS2 cases: ≤ PS1 cases; HR = 2.32, 95% CI: 1.14–4.73, $p = .020$].

d) Causal factors and factors for poor prognosis (fatal case) found in this investigation

These factors found are considered to be extremely valuable for further safety assurance in administrating this product. On the other hand, it is difficult to conclude with the result of this investigation that these risk factors are specific to this product for the following reasons: Some factors are similar to those of lung cancer. This investigation only targeted cases treated with this product. Furthermore, the number of evaluated cases for factors of poor prognosis (fatal case) was 101, which was small.

e) Blood concentration

No relationship between steady-state trough blood concentration of this product and acute lung disorders/interstitial pneumonia was found.

(3) Safety measures based on the result of prospective study

As for risk factors and factors for poor prognosis of acute lung disorders/interstitial pneumonia, cases of ≥ PS2 have been investigated. Furthermore, "PRECAUTIONS" was revised as it was found that the incidence and mortality rate due to acute lung disorders/interstitial pneumonia tended to increase with deterioration of general conditions when stratified by PS level.

① "While cases with fatal cases due to acute lung disorders and interstitial pneumonia have been reported regardless of patients' general conditions, the incidence and mortality rate tend to be increased particularly for patients with poor general conditions. Caution should be exercised when administrating this drug such as by monitoring patients' condition" was added to the section of [Warning].

② "Patients with poor general condition" was added to the section of [Careful Administration]

(4) Closing comments

The incidence and risk factors have been uncovered to some degree from the result of this investigation. Needless to say, early detection and rapid appropriate care lead to improvement of patients' prognosis. Healthcare professionals should carefully read the package insert for proper use. In particular, the patient should be sufficiently monitored through hospitalization or under similar conditions of control for at least 4 weeks from the start of administration as a general rule. Also, patients should be informed of subjective symptoms and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Moreover, if adverse reactions such as interstitial pneumonia etc. occur, healthcare professionals should immediately report these adverse reactions to the Pharmaceutical and Food Safety Bureau of Ministry of Health, Labour and Welfare in accordance with the article 77-4-2-2 of the Pharmaceutical Affairs Law as well as cooperation in the collection of information on the appropriate use of pharmaceuticals conducted by companies in accordance with the article 77-3-2 of the Pharmaceutical Affairs Law.

3

Safety measures for blood glucose monitoring kits

(1) Introduction

The basic treatment for diabetes consists of alimentotherapy, ergotherapy, and pharmacotherapy to control blood glucose as well as to prevent any complications. Blood glucose level and HbA_{1c} are measured as the parameter for blood glucose control. Recently, simplified self-monitoring blood glucose meter has been developed allowing blood glucose test at home.

Cases of hypoglycaemia in patients using simplified self-monitoring blood glucose meter have been recently reported. Consequently, MHLW had analyzed the causation etc. and revised the package insert as a safety measure. In this section, the content of the safety is presented.

(2) Types and principles of blood glucose measurement

Currently, there are glucose dehydrogenase (GDH) method, hexokinase (HX) method, glucose oxidase (GOD) method etc. for measuring blood glucose [1)]. As for GDH method, there are types using pyrrolo-quinoline quinone (PQQ), nicotinamide adenine dinucleotide (NAD), or nicotinamide adenine dinucleotide phosphate (NADP) as coenzyme. It is a method using β-D-glucose conversion to D-glucono-δ-lactone with simultaneous reduction of each coenzyme. Specifically, glucose concentration is measured based on the principle of absorbance determination of β-NAD (P) H, measurement of electric current generated at oxidoreduction reaction, and absorbance determination of discolored substances due to reduction (**Figure 1**).

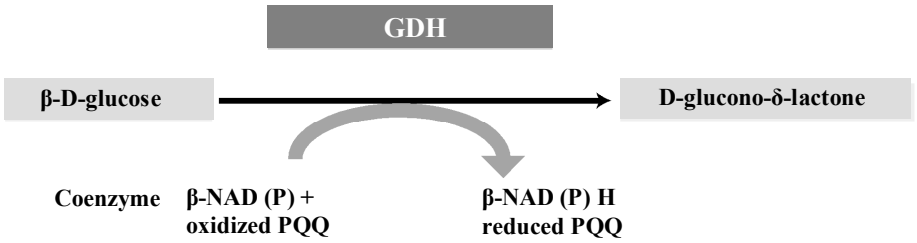

Figure 1 Measuring principle

(3) Reported cases

Two cases by healthcare providers and single case by a company of hypoglycaemia in patients using simplified self-monitoring blood glucose meter have been reported since June 2004.

Table 1 gives Case summary.

Table 1

No.	Case summary
1	The patient measured blood glucose level using simplified self-monitoring blood glucose meter during administration of maltose-containing infusion and adjusted the insulin dose based on the measured value, resulting in hypoglycaemia accompanied with consciousness disturbed due to overdose. Hypoglycaemia was recovered with administration of glucose. The measured value was high at around 100 mg/dL compared to that of central laboratory at the institution.
2	When the patients' blood was measured by simplified self-monitoring blood glucose meter during intravenous infusion of nutrient, it showed 557 mg/dL while it was 187 mg/dL by automatic analyzer.
3	The patient who might have been given maltose-containing infusion during surgery manifested higher value (164 mg/dL) than actual value (11 mg/dL by central laboratory).

(4) Items discussed etc.

First of all, blood glucose monitoring kits used in the reported cases were examined. Every case was found to have used blood glucose monitoring kits based on GDH method as the measuring principle. Second, coenzymes used were studied and each found to be PQQ.

Under the section "Interfering Substance" in the package insert of blood glucose test kits (**Table 2**) using the GDH enzyme method as the measuring principle with PQQ as coenzyme, it is already stated that it shows higher blood glucose levels than the actual value when measuring a specimen containing high maltose, icodextrin, galactose, or xylose [2)]. Therefore, it is likely that these reported cases were due to using this particular test kit.

On the other hand, the effect of the saccharides such as maltose on the blood glucose monitoring kit using the same measuring principle of the GDH method with NAD or NADP as a coenzyme, has been unknown to date. To confirm that the effect by maltose etc. on the value measured by the GDH method is due to certain types of coenzymes, specimens of each product added with various types of coenzymes were measured. As a result of the measurement, measured values by blood glucose testing using NAD or NADP as coenzyme were not affected (**Table 3**).

Table 2 List of major blood glucose test reagent (GDH method with PQQ as coenzymes)

Japan Association of Clinical Reagents Industries (JACR)

	Reagent brand name	Measuring principle	Enzyme name	Co-enzyme	Manufacturer (importer)	Applicable device name	Manufacturer (importer)
1	FreeStyle Kissei Sensor	GDH electrode method	GDH	PQQ	Nipro Corporation	Freestyle Kissei Meter	Nipro Corporation
2	Nipro FreeStyle Sensor	GDH electrode method	GDH	PQQ	Nipro Corporation	Nipro Freestyle Meter	Nipro Corporation
3	Accu-Chek Compact Drum II	GDH colorimeter method	GDH	PQQ	Roche Diagnostics K.K.	Accu-Chek Compact	Roche Diagnostics K.K.
4	Accu-Chek Active Sticks	GDH colorimeter method	GDH	PQQ	Roche Diagnostics K.K.	Accu-Chek Compact	Roche Diagnostics K.K.
5	Advantage Test Strips S	GDH electrode method	GDH	PQQ	Roche Diagnostics K.K.	Accu-Chek Comfort advantage Advantage II	Roche Diagnostics K.K.
6	Glutest Neo Sensor	GDH electrode method	GDH	PQQ	Matsushita-Kotobuki Electronics Industries, Ltd.	Glutest Neo	Matsushita-Kotobuki Electronics Industries, Ltd.
7	G sensor	GDH electrode method	GDH	PQQ	Matsushita-Kotobuki Electronics Industries, Ltd.	GlucoCard G meter	Matsushita-Kotobuki Electronics Industries, Ltd.
8	GASTAT-mini Sensor Card for glucose measurement	GDH electrode method	GDH	PQQ	Techno Medica Co., Ltd.	GASTAT-mini sensor card (multi-item analyzers)	Techno Medica Co., Ltd.

Note) GDH: glucose dehydrogenase, PQQ: pyrrolo-quinoline quinine As of September, 2004

Table 3 Cross-reactivity test result (the effect on measured blood glucose level by each additive glucose in glucose solution)

Normal saline solution added		Additive-free	Maltose added					Galactose added				
Concentration of added glucose (mg/dL)		0	120	240	360	480	600	60	120	180	240	300
Reagent	Coenzyme	Measured results (average: mg/dL)						Measured results (average: mg/dL)				
A	NAD	97	97	98	97	98	97	97	97	96	97	97
B	NAD	97	97	97	98	98	97	97	97	98	97	97
C	NAD	98	98	100	99	99	99	98	99	99	99	99
D	NAD	96	97	97	97	96	97	97	98	96	96	96
E	NAD	98	98	100	99	99	99	100	99	99	99	100
F	NADP	97	98	97	98	98	98	98	98	98	98	98
G	NAD	99	99	99	98	100	99	97	98	99	100	98
H	NAD	165	165	164	167	168	168	166	169	163	166	164
I	PQQ	104	159	205	257	294	337	156	211	252	286	343

Normal saline solution added		Additive -free	Xylose added				
Concentration of added glucose (mg/dL)		0	40	80	120	160	200
Reagent	Coenzyme	Measured results (average: mg/dL)					
A	NAD	97	99	103	105	107	110
B	NAD	96	100	103	105	107	110
C	NAD	99	101	103	105	107	109
D	NAD	97	97	97	96	97	98
E	NAD	99	99	99	100	100	100
F	NADP	98	99	98	98	98	98
G	NAD	99	103	109	116	119	125
H	NAD	164	162	162	165	170	172
I	PQQ	100	133	153	188	239	258

Normal saline solution added		Additive -free	Maltotriose (G3) added					Maltotetraose (G4) added				
Concentration of added glucose (mg/dL)		0	60	120	180	240	300	60	120	180	240	300
Reagent	Coenzyme	Measured results (average: mg/dL)						Measured results (average: mg/dL)				
A	NAD	97	96	96	97	97	96	97	97	98	97	97
B	NAD	96	97	98	97	97	98	99	97	97	97	98
C	NAD	99	99	100	99	98	98	100	99	99	99	99
D	NAD	96	98	97	97	97	97	96	97	98	97	96
E	NAD	98	99	99	99	99	100	100	99	100	99	100
F	NADP	98	98	97	98	98	98	99	98	99	98	98
G	NAD	99	99	98	99	99	99	99	99	98	100	100
H	NAD	160	159	158	164	159	161	159	162	163	160	170
I	PQQ	101	123	142	164	180	198	119	130	145	155	170

Normal saline solution added		Additive -free	Maltopentaose (G5) added					Maltohexaose (G6) added				
Concentration of added glucose (mg/dL)		0	60	120	180	240	300	60	120	180	240	300
Reagent	Coenzyme	Measured results (average: mg/dL)						Measured results (average: mg/dL)				
A	NAD	96	97	97	97	97	97	97	97	97	97	98
B	NAD	97	96	97	97	97	98	97	97	97	97	98
C	NAD	99	99	99	99	99	100	99	99	99	99	99
D	NAD	97	96	97	97	97	96	96	96	97	97	96
E	NAD	98	99	99	98	99	100	99	99	100	98	99
F	NADP	98	99	99	99	98	99	98	99	99	98	98
G	NAD	99	99	100	98	99	100	99	99	99	99	100
H	NAD	163	164	163	163	167	164	165	162	164	165	163
I	PQQ	102	111	119	131	139	150	110	117	125	134	145

Note) 97 mg/dL as glucose concentration. Note that H is corrected for measuring whole blood sample, hence, measured glucose value is higher in aqueous solution sample.

Note) I is measured by a system using glucose dehydrogenase (EC1.1.5.2) with PQQ as coenzyme.

(5) Safety measures

MHLW has checked the package insert of all the blood glucose monitoring kits based on GDH method as the measuring principle except for the ones using NAD or NADP as coenzyme and description regarding the influence on measured blood glucose value by maltose etc, was confirmed in every package insert. Although it is considered that precaution is taken to a certain degree, MHLW has decided to add the following items to call for a further alert, based on the aforementioned case reports and the result of investigation regarding the influence of coenzyme by GDH method for further attention.

The following patients should not use with this product, since overestimation of blood glucose levels may occur.
Patients receiving infusions etc. containing maltose Patients receiving dialysis solution containing icodextrin Patients undergoing galactose tolerance test Patients undergoing a xylose absorption test

As for the package inserts of infusions etc. containing maltose, it is included that reagents and meter with the descriptions of influence by maltose in the package inserts should not be used for measuring blood glucose of a patient with this drug, since blood glucose measurement using these kits will be affected by maltose and there are cases of overestimation of blood glucose levels are indicated.

Note that same revision was also made in the package insert of blood glucose meter using these kits as its reagent.

(6) Closing comments

Home-care has been developed in recent years, subsequently, it is anticipated that there will be more cases where peritoneal dialysis and infusion treatment are implemented at home in the future. Using these kits in home care patients with diabetes mellitus should be avoided when self-monitoring blood glucose level during peritoneal dialysis or infusion treatment since the blood glucose monitoring kits based on GDH method (except for ones using NAD or NADP as its coenzyme) as the measuring principle may induce overestimation of blood glucose levels .

Furthermore, simplified self-monitoring blood glucose meter is originally designed to be used for self-monitoring of blood glucose levels at home etc. under supervision by a physician. However, it has been known to be used at emergency or during infusion etc. treatment as it is easily used. Again, simplified self-monitoring blood glucose meter is designed to be used for the purpose of gaining the control of daily blood glucose levels. Treatment at emergency or during infusion etc. treatment should be conducted based on the blood glucose levels measured by the automatic analyzer.

<References>

1) Takimoto Junzaburo: Testing Method for Diagnosis of Diabetes Mellitus. Medical Technology, 30 (13): 1478-1479 (2002) (In Japanese)
2) Sano Syunichi et al.: Influence of Maltose on Self-monitoring Blood Glucose Meter Used in Japan. Practice 21 (1): 91-96 (2004) (In Japanese)