Pharmaceuticals and Medical Devices Safety Information

No. 212 April 2005

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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).

Published by
Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

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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. 212 April 2005

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

[Outline of Information]

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1	**Results of investigation by the Gefitinib review meeting**	*P*	With respect to the ISEL study implemented overseas in accordance with FDA's conditions for approval, Gefitinib demonstrated statistically significant improvement in terms of tumor shrinkage. However, with respect to survival time which was a primary endpoint, it was reported that the drug did not show a statistically significant survival benefit. Based on these results, a meeting of the Gefitinib Investigative Committee was held in order to consider the effect of these studies toward the drug's clinical utility in Japan. In this section, an overview etc. of the results produced by this committee is presented.	3
2	**Overview of the notifications for self-inspection etc. issued from April 2004 to February 2005**	*P*	An overview of the notifications issued between April 2004 and February 2005 for revisions to be made to the package inserts and self-inspections relating to the safety of medical devices, as post-marketing safety measures for medical devices is presented in this safety information. Hereafter, outlines of notifications on medical devices will also be published as needed in each edition of Pharmaceuticals and Medical Devices Safety Information.	14
3	**Request for cooperation in Early Post-marketing Phase Vigilance**		When new drugs come on to the market, we have only limited information about their safety. The new drug is tested in clinical trials. Since these trials are generally restricted in terms of number of patients, concomitant drugs, complications, age, and other factors, this information has its limitations. However, once a new drug is on the market, as the number of drug users dramatically increase and as the conditions of drug users become much more variegated compared to the patients during the clinical studies, serious adverse reactions etc. which were not made apparent at the clinical studies have been known to occur. In acknowledgment of these unknown characteristics of new drugs, the early post-marketing phase vigilance system is a particularly important system in post-marketing safety measures, to promote particular caution in the use of a new drug during the first 6 months of its marketing, and to strengthen the information gathering system in the event that serious adverse reactions occur. MHLW hopes that healthcare professionals including physicians, dentists, and pharmacists understand the objective of early post-marketing phase vigilance and ask for your proactive cooperation in reporting such adverse reactions.	24

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

1

Results of investigation by the Gefitinib review meeting

Active ingredient	Active ingredient	Brand name (company name)
Brand name (company name)	Gefitinib	Iressa Tablets 250 (AstraZeneca K.K.)
Therapeutic category	Miscellaneous antineoplastics	
Indications	Inoperable or recurrent non-small cell lung cancer	

(1) Introduction

Gefitinib (brand name: Iressa Tablets 250) is an anticancer drug indicated for the treatment of inoperable or recurrent non-small cell lung cancer and was approved on July 5, 2002.

In accordance with the conditions for the drug's approval, multicenter unblinded randomized phase III trial currently has been conducted in Japan to compare the survival times of gefitinib with docetaxel in patients with untreatable non-small cell lung cancer who had received at least 1 or 2 chemotherapy regimens.

While gefitinib has been approved in 36 countries as of April 2005, the results of an initial analysis in December 2004 of the ISEL (IRESSA Survival Evaluation in Lung cancer) study implemented overseas in accordance with FDA conditions for the approval showed statistically significant improvement in tumor shrinkage, but did not show statistically significant benefit in survival time as aprimary endpoint in the overall population. Based on these results, the Gefitinib review meeting was held to consider the effectiveness in clinical use of gefinitib in Japan. The summary of the review is as follows.

(2) Outline of the ISEL study

The ISEL study was a randomized double-blind placebo-controlled phase III clinical study in patients with recurrent or advanced non-small cell lung cancer who had failed one or two prior chemotherapy regimens. This study was conducted in 28 countries except Japan.

① Study period: July 15, 2003–August 2, 2004

② Patients: 1692 cases (1129 cases with gefitinib, 563 cases with placebo)
210 centers in 28 countries

③ Primary endpoint: survival time

④ Secondary endpoints: period until change in treatment, response rate, QOL, EGFR development, EGFR gene mutations and other biomarkers, and safety

(3) Assessment of ISEL study results and current responses to gefitinib use

The review meeting discussed the result of the initial analysis of the ISEL study on January 20, 2005 and summarized their conclusions in "Opinions relating to initial analysis results of the ISEL study". In order to conclude the effectiveness of this study on the clinical use of gefitinib in Japan, the more detailed analysis of the results was needed.

Furthermore, a subgroup analysis suggested that the drug contributed to prolonging survival time in oriental people, although Japanese were not included in the target population; EGFR gene mutation in non-small cell lung cancer influenced the responsiveness of the tumor to the drug; and the ratio of such

genetic alterations was higher in Japan compared to in the United States. Considering these findings, it was seemed that the need to discuss measures to restrict the drug's use at this point in time was lacking. The onset of serious adverse reactions such as interstitial pneumonia should be sufficiently monitored for at least 4 weeks after the start of administration under hospitalization or similar conditions of control, and while continuing to observe safety measures written in the package insert, the drug should be administered under the care of a physician sufficiently experienced in lung cancer chemotherapy. It was recognized suitable to promote such appropriate use of this drug.

Later, as the ISEL study results were submitted by the pharmaceutical company in March this year, this meeting was convened 3 times on March 10, 17, and 24 of this year to consider follows; the results of this detailed analysis of ISEL study, the findings relating to EGFR gene mutation which was brought up at the review meeting in January this year, and the "Guidelines for gefitinib use" (Japan Lung Cancer Society) which was revised by the request from Ministry of Health, Labour and Welfare were reviewd and the following conclusions were derived.

1) ISEL study results

After assessing the materials submitted by the pharmaceutical company, it was confirmed that the ISEL study was a well-controlled trial. And then, the results of detailed analysis of the ISEL study were reviewed and the following were confirmed.

a) In an analysis of all cases, although a statistical significant difference in tumor shrinkage (response rate) was confirmed in a comparison of the gefitinib group and the placebo group, a statistically significant difference was not confirmed in terms of the primary endpoint, survival time, analyzed in accordance with the analytical method written in the protocol.

b) A subgroup analysis in oriental people suggested that the administration of gefitinib contributed to prolonging survival time. Robustness of the results of subgroup analysis was confirmed.

2) Clinical application of EGFR gene mutations

Recent findings relating to EGFR gene mutations and the efficacy of gefitinib were considered and the following conclusions were made.

a) EGFR gene mutation is an important factor in predicting the efficacy of gefitinib (tumor shrinkage).

b) Regarding the EGFR gene mutation test:
   ① Standard measurement and assessment methods have not been established and falsely-negative results may have been derived from the EGFR gene mutation test
   ② Although a few, there were cases in which EGFR gene mutation was not confirmed which indicates tumor shrinkage.

Based on the above findings, current measurement and assessment methods did not produce sufficiently conclusive grounds for not conducting gefitinib treatment even for cases in which EGFR gene mutation was not confirmed.

3) Current response to gefitinib use

After the consideration by this committee of the above matters 1), 2), and the "Guidelines for gefitinib use" which were revised in March of this year, it was determined suitable that conventional safety measures continue to be implemented and that, for the time being, the government and industry should take the following measures.

a) In promoting proper use of gefitinib, Japan should institute measures to disseminate this guideline among healthcare providers and patients.
   ① The pharmaceutical company should be instructed to indicate in their package inserts that this guideline should be referred to when using gefitinib.
   ② The pharmaceutical company should be instructed to disseminate this information by distributing this guideline to healthcare professionals.
   ③ In addition to disseminating this guideline to healthcare providers through related societies and organizations etc., the information in this guideline should also be provided to patients through the Pharmaceuticals and Medical Devices Information website etc.

b) While the pharmaceutical company should make greater efforts to grasp patient information, they should also make efforts to clarify the relationship between the efficacy of gefitinib and relative gene mutation, as well as to establish EGFR gene mutation test methods etc in cooperation with relevant academic societies etc. The results of their efforts should be proactively released to the public and information should be provided to healthcare providers and patients.

c) In order to assess the efficacy of gefitinib in life prolongation of Japanese patients, it will be necessary to obtain the results from the unblinded randomized intergroup study currently being conducted in Japan using docetaxel as a control. Therefore, the pharmaceutical company should make efforts toward a speedy conclusion to these studies.

d) The pharmaceutical company should make efforts to clarify the cause for the onset of acute pulmonary disorders and interstitial pneumonia and to establish methods of prevention. The results should be proactively released to the public and information should be provided to healthcare providers and patients.

(4) Responses based on the conclusions of the Gefitinib review meeting

Based on the conclusions of this investigative committee, MHLW requested that revisions be made to the "PRECAUTIONS" section as well as to disseminate the "Guidelines for gefitinib use" to healthcare providers through related societies and organizations etc. for promoting the proper use of gefitinib.

① "Refer to the latest information on the drug such as the Japan Lung Cancer Society's 'Guidelines for gefitinib use' when administering this drug" etc. was added to the [Important Precautions] section.

② "In a randomized double-blind placebo-controlled phase III clinical study conducted overseas targeting recurrent or advanced non-small cell lung cancer in patients who had received at least 1 or 2 chemotherapy regimens, although a statistically significant difference was confirmed in terms of tumor shrinkage, a statistical significant difference was not confirmed in terms of effect on life prolongation among all targeted patients (HR = 0.89, p = 0.09, median: 5.6 months vs 5.1 months) and in the adenocarcinoma patient group (HR = 0.84, p = 0.09, median: 6.3 months vs 5.4 months)" was added to the [Other Precautions] section.

(5) At the end

When considering treatment with this drug, it is important that physicians thoroughly read the package insert, refer to the latest information on the drug such as the "Guidelines for gefitinib use", provide sufficient explanation to patients on the drug's efficacy and safety etc. such as the ISEL study results, and obtain patient consent.

In addition, in the case of adverse events such as interstitial pneumonia etc. for which a causality to the drug could not be denied, promptly report these adverse events to the Safety Division of the Pharmaceutical and Medical Safety Bureau in Ministry of Health, Labour and Welfare in accordance with article 77-4-2-2 of the Pharmaceutical Affairs Law.

The "Guideline for gefitinib use" can also be obtained from the Pharmaceuticals and Medical Devices Information website of the Pharmaceuticals and Medical Devices Agency.
(http://www.info.pmda.go.jp/happyou/happyou_index.html) (In Japanese)

Moreover, the materials which were used at the Gefitinib Investigative Committee can be obtained from the MHLW's website.
(http://www.mhlw.go.jp/shingi/other.html#iyaku) (In Japanese)

(References)

The Japan Lung Cancer Society
"Committee for the drafting of guidelines for gefitinib use"

Guideline for gefitinib use

Prepared on February 19, 2005
First revision: March 2, 2005
Second revision: March 15, 2005

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Gefitinib (Iressa®) is an anticancer drug which exhibits antitumor activity through its EGFR tyrosine kinase inhibitory effect. In the phase II multinational study (IDEAL-1; references 1) in which Japan participated, in patients who have failed prior chemotherapy regimens including a platinum drug or patients with recurrent non-small cell lung cancer showed a 27.5% response rate among Japanese. On July 5, 2002 Ministry of Health, Labour and Welfare (hereafter, MHLW) approved the drug indicated for the treatment of inoperable or recurrent non-small cell lung cancer ahead of all other countries. Later, on May 5, 2003, the U.S. Food and Drug Administration (FDA) approved monotherapy of gefitinib in patient with advanced non-small cell lung cancer who had been refractory to standard chemotherapies. It has been approved in 35 countries and regions to date.

In Japan, serious interstitial pneumonia and acute lung disorder which were thought to have been associated with the administration of this drug during post-marketing were reported one after another and this became a social issue. As of December 28, 2004, according to the "Status of adverse drug reaction onset such as acute lung disorder and interstitial pneumonia etc. for which a causality to gefitinib is suspected" reported to MHLW and Pharmaceuticals and Medical Devices Agency (hereafter, PMDA), 1473 cases have been reported, of which 588 patients have died. The estimated cumulative number of patients treated with gefitinib reported to MHLW during the same period by AstraZeneca K.K. (hereafter, AstraZeneca) was 86800 patients. On October 15, 2002, a "Dear Healthcare Professional Letter" on interstitial pneumonia and acute lung disorder due to this drug was issued by the request of MHLW. On December 25, 2002, MHLW held the "First review meeting on safety of gefitinib" which was followed on the 26th by the issuance of "Notification for the measures based on the investigative results". The review meeting was also convened on May 2, 2003. AstraZeneca organized an "Expert meeting on acute lung disorder and interstitial pneumonia by gefitinib" which analyzed cases of acute lung disorder and interstitial pneumonia suspected to have causality to this drug. The results were reported on March 26, 2003 (references 2).

In August 2004, AstraZeneca reported on its "Results and discussion regarding the prospective study (special study) of Iressa® Tablets 250" (references 3). According to this report, among the cases registered between June and December 2003, the review was conducted toward 3322 cases for safety assessment. The "review results on acute lung disorder and interstitial pneumonia in post-marketing phase vigilance" found a "5.81% incidence of acute lung disorder and interstitial pneumonia (193 out of 3322 cases)" and a "2.3% incidence of deaths (75 out of 3322 cases)". The multivariate analysis of onset factors for acute lung disorder and interstitial pneumonia showed that PS>2, having smoking history, complicated interstitial pneumonia, and having chemotherapy history were significant factors. The multivariate analysis of poor prognostic factors (outcome of death) for acute lung disorder and interstitial pneumonia showed that men and PS>2 were significant factors. The package insert of this drug was revised several times based on these reports and analyses. The 10th revised edition of February 2005 is presently in use.

The Japan Lung Cancer Society established the "Review committee for the proper use of gefitinib" for the purpose of summarizing opinions on the proper use of gefitinib. It prepared a guideline regarding the use of gefitinib in clinical trials and in the clinical practices mainly for the safety. The guideline was published as the "Statements regarding 'gefitinib'" in the journal issued by the society, *Lung Cancer* (Volume 43, No. 6, October 2003) (references 4).

In the spring of 2004, a report from the United States which suggested EGFR gene mutations were predictive factors for tumor response to gefitinib attracted attention (references 5, 6). It was also suggested that the background factors of cases presenting EGFR gene mutations were predictive factors for response which have already been clinically demonstrated. Those factors are non-smokers, adenocarcinoma, women, and Japanese (oriental people) (references 7) in the response to this drug.

On December 17, 2004, AstraZeneca (headquarters, England) publicized the results of initial analysis of a clinical study (ISEL; Japanese institutions did not participate in this study) subjected to 1692 cases with survival time as the primary endpoint. It was shown in this study that gefitinib

"in an analysis of all cases (hazard ratio 0.89, p = 0.11, survival time median 5.6 vs 5.1 months) and adenocarcinoma cases (hazard ratio 0.83, p = 0.07, survival time median 6.3 vs 5.4 months), survival time did not significantly prolonged compared to the placebo". On the other hand, a subset analysis of 342 oriental people suggested that survival time improved in the gefitinib group (survival time median 9.5 vs 5.5 months).

As well, a subset analysis of 374 non-smokers suggested that survival time was improved in the gefitinib group (survival time median 8.9 vs 6.1 months). However, when the target for analysis was limited to oriental smokers (201 cases), there was no difference with the placebo group (survival time median 5.7 vs 6.3 months). Based on these results, FDA issued a statement that appropriate regulatory measures such as a withdraw of Iressa from the market might be taken. Meanwhile, AstraZeneca announced it would withdraw its application for approval to the European Agency for Evaluation of Medicinal Products (EMEA). In Japan, MHLW convened the "Gefitinib review meeting" on January 20, 2005 and published the review results as "Opinions regarding the results of primary analysis for the gefitinib ISEL study." 2 main conclusions drawn: 1) it is necessary to wait for detailed analysis results from the ISEL study; 2) the need to discuss measures to restrict the drug's use at this point in time was lacking. On March 4, 2005, FDA deliberated on the results of the ISEL study at a hearing called the "Oncologic Drugs Advisory Committee" (ODAC).

Within this backdrop, in February 2005 the Safety Division of Pharmaceutical and Medical Safety Bureau in MHLW requested the Japan Lung Cancer Society to make revisions to the guideline for gefitinib use in clinical practice based on recent findings. In response, on February 17, 2005, the president of the Japan Lung Cancer Society organized the "Committee for the drafting of guidelines for gefitinib use" (hereafter, drafting committee). Based on the "Statements regarding 'gefitinib'" by this society in October 2003 and on subsequent findings, the committee identified groups with a high potential to derive benefits from gefitinib, and from the standpoint of improving the benefit-risk balance of the drug used in clinical practice, drew up the "Guideline for gefitinib use in clinical practice".

In addition, it should be brought to your attention that this is a tentative guideline which was quickly drafted during a short time in the backdrop of the changing situation of gefitinib on the world stage.

Guideline for gefitinib use in clinical practice

● Indications

1. "Inoperable or recurrent non-small cell lung cancer" which is an indication of this drug specified in "Indications" of the package insert of this drug should be strictly complied.
2. As described in "Precautions of Indications" in the package insert of this drug, as "1. Efficacy and safety in patient without history of chemotherapy has not been established; and 2. Efficacy and safety in patient with postoperative adjuvant therapy has not been established," this drug should not be used in clinical practice to treat such cases.

   <Note> Regarding item 1, in Japan the results of at least 3 clinical phase II trials have been published (references 8–10) with a response rate of approximately 30%. In 2 trials for which median survival time (MST) is identified, MST was 14.5 months and 10.0 months. On the other hand, a 10% death rate from acute lung disorder was reported in 1 trial. From the above, at this point in time it is suggested that the evidence to deny "Efficacy and safety in patients without chemotherapy" in the package insert has not been enough.
3. Patients groups most likely to derive clinical benefit (prolonging of life, improvement of symptoms, tumor shrinkage) from the administration of gefitinib have begun to be ascertained. These groups include adenocarcinoma, women, non-smokers, Japanese (oriental people), and cases exhibiting EGFR gene mutation. In the future, it is recommended that this drug be administered toward these patient groups who are most likely to benefit from the administration of this drug.

   <Note 1> During the phase I trial for this drug in Japan (references 11), it was reported that

among the 31 various malignant tumor cases, all of 5 cases showed PR were non-small cell lung cancer cases, all histological cancer types were cases of adenocarcinoma, and 4 cases were women. In the IDEAL-1 Japanese subset analysis (references 12), MST in women vs men was 414 days vs 309 days, and MST in adenocarcinoma vs non-adenocarcinoma patients was 406 days vs 275 days. Although a statistical significant difference was not demonstrated, survival curves for both groups showed large divergence. Similar results were shown in clinical practice (references 13-15). These results can be raised as grounds for this guideline.

<Note 2> Based on early reports from the United States (references 5, 6, and 16) suggesting that EGFR gene mutation is a predictive factor for response to gefitinib, there are researchers who assert their belief that the administration of gefitinib should be limited to cases exhibiting EGFR gene mutation. However, the following points are also true: ① a standard method of measuring and assessment for EGFR gene mutation has not been established. Therefore, it is possible that the detection rate will differ depending on the method of detection, and it is often difficult to obtain samples of non-resectable lung carcinoma with little intermixture of normal cells; ② there are cases which require several weeks for measurement; ③ there are a limited number of research institutes capable of conducting analysis, and making the analysis process more routine would be difficult at this point in time; ④ it is possible that there are gene mutations other than the exons that code for the EGFR-TK domain; ⑤ apart from EGFR gene mutations which heighten sensitivity to gefitinib, gene mutations which cause resistance to gefitinib have also been discovered (references 17, 18); ⑥ it is possible that there are other genes involved in responsiveness to the drug other than the EGFR gene; ⑦ there is a strong correlation between the clinical efficacy of this drug and EGFR gene mutation and there is no doubt that EGFR gene mutation is an important predictive factor for response to gefitinib. However, a perfect correlation between gene mutation and responsiveness was not indicated from the research conducted in Japan (references 19-23). For these reasons, it is apt to judge that it is not realistic or certain at this point in time to warrant conducting measurements for the presence or absence of EGFR gene mutations beforehand in all cases to be administered this drug, and to set parameters for patients who will receive this drug.

4. As the efficacy and safety of the concurrent administration of this drug together with other antitumor drugs or radiation therapies has not been established, this drug should be given as a monotherapy in clinical practice.

   <Note> The benefit of added this drug was not shown from 2 phase III studies (INTACT, references 24, 25; Japanese institutions did not participate in this research) to ascertain the significance of adding gefitinib to standard chemotherapies targeting patients with previously untreated advanced non-small cell lung cancer. The onset of serious myelosuppression from the concurrent administration of vinorelbine was reported (references 26, 27).

5. As criteria for selecting cases for gefitinib administration, the case selection and exclusion criteria (attachment 1) for the multinational phase II study on this drug in which Japan participated (references 1) should be referred to. Another source which should be used as reference is the case selection and exclusion criteria for the clinical trial which was directed by physicians and safely implemented in Japan. As the safety in administering the drug in cases other than these has not been investigated, as a general rule at this point in time, the drug should not be administered in cases other than for clinical studies.

6. When administering this drug in cases presenting known risk factors for the onset of acute lung disorder and interstitial pneumonia from this drug, such as cases with poor general condition of ≧PS2, patients with a smoking history, cases complicated by interstitial pneumonia (idiopathic pulmonary fibrosis, radiation pneumonitis, drug-induced pneumonia etc.), male patients, patients with hypoxaemia, pneumoconiosis, and squamous cell carcinoma, the drug should only be administered when it is determined that the benefits derived for the patient outweigh the risks.

   <Note> Refer to the risks factors for the onset of acute lung disorder and interstitial pneumonia,

and the poor prognostic factors after onset cited in detail in references 2, 3, and 13.

7. This drug should also be administered by physicians with ample experience in lung cancer chemotherapy and at medical institutions capable of carrying out sufficient measures in case of emergencies at time of administration. In addition, it is desirable that the drug be administered in an environment where the patient can receive appropriate advice from a specialist in interstitial pneumonia.
8. After thoroughly explaining the purpose of administration of this drug, the administration method, anticipated effects (including ISEL study results), adverse reactions (including the fact that there have been cases of onset of serious interstitial pneumonia and acute lung disorder, as well as cases resulted in death), the presence/absence of alternative therapies, and the benefit and risk of such alternative therapies, the patient's consent given by his/her own volition should be obtained in writing.
9. The drug should be administered only when all of the above conditions have been met.

● Precautions at time of administration

1. Caution should be exercised when administrating this drug for onset of all symptoms of acute lung disorder and interstitial pneumonia including pyrexia, dry cough, shortness of breath, and dyspnoea etc. Careful auscultation is important in diagnosing interstitial pneumonia. As well, oxygen saturation (SpO_2) measurements and chest X-rays should be conducted as needed.
   <Note> A detailed explanation can be found in referencs 2.
2. An explanation should be provided to the patient in advance as to the significance of the aforementioned subjective symptoms. If these symptoms are presented, the patient should be instructed to seek immediate examination from the physician (medical institution) in charge.
   <Note> As it goes without saying that the patient will become aware of these subjective symptoms before anyone else, it is important to reaffirm the importance of collaboration between all healthcare providers including the patient and physician for the early detection of acute lung disorder and interstitial pneumonia.
3. The medical institution should prepare a system which will make it possible for patients complaining of the above symptoms to be examined at all times.
4. Item 2 in the "Warning" section of this drug's package insert states "… as there are many cases of acute lung disorder or interstitial pneumonia onset during the initial stage of the drug's administration which have resulted in death, the patient should be sufficiently 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." This "Warning" should be strictly observed when this drug is to be administered.
   <Note> Refer to references 3. In addition, as a high incidence of cases resulting in death due to the onset of acute lung disorder and interstitial pneumonia within the first 1 to 2 weeks after the start of administration have been reported (references 13), close monitoring through hospitalization is strongly recommended especially during the first 2 weeks after the start of administration.
5. If the above subjective symptoms are observed, promptly undergo plain chest X-ray, chest CT (HRCT, as soon as possible), arterial blood gas analysis (especially be most cautious of AaDO2), and DLco measurements etc. to ascertain the presence/absence of acute lung disorder or interstitial pneumonia. As comparison with measurements taken before drug administration is important for discernment, it is desirable that these tests be conducted before drug administration as well.
6. As it is often the case that this drug's therapeutic effect is confirmed at the early stages of administration (references 28), in the event that there is no improvement in subjective symptoms complicating the lung cancer or if no tumor shrinkage is confirmed through X-ray even after 1 month and more since the start of administration, the decision to continue or

discontinue treatment with this drug should be carefully determined through comprehensive reassessment of the patient's general condition, patient wishes, and the presence/absence of risk factors for acute lung disorder and interstitial pneumonia.

● Measures for the onset of acute lung disorder and interstitial pneumonia

1. If acute lung disorder and interstitial pneumonia developed, immediately discontinue administration of this drug.
2. There have been sporadic reports of corticosteroid hormones being effective in some cases of acute lung disorder and interstitial pneumonia. If administration of corticosteroid hormones is not contraindicated, pulse therapy of methylprednisolone at 500 to 1000 mg for 3 days should be considered. Moreover, for cases showing improvement through continued administration of corticosteroids, the dosage should be decreased by degrees carefully.
3. The efficacy of immunosuppressive agents is not certain.

Addendum) This guideline will be revised as necessary according to new findings on gefitinib efficacy factors and ILD onset factors etc.

Appendix 1 (reference)
Case selection and exclusion criteria for the "Randomized double-blinded parallel-group multicenter phase II study to consider the efficacy of ZD1839 (IRESSATM) 250 mg/day and 500 mg/day in the treatment of advanced non-small cell lung cancer in patients with a history of 1 or 2 regimens of chemotherapy (at least 1 regimen containing a platinum drug)."

Selection criteria

1. Patients with Stage III locally advanced (or metastatic) NSCLC which cannot be treated through surgery or radiation therapy or stage IV. Patients histologically or cytologically confirmed as having NSCLC.
2. Patients who received 1 or 2 regimens of chemotherapy (at least 1 regimen containing a platinum drug) and exhibited recurrence or resistance.
3. Patients with a distinct focal site with 1 and more lesion capable of bidirectional measurement. Or, patients without a distinct focal site, but with 1 and more lesion which can be assessed through X-ray.
4. Patients with WHO Performance Status (PS) of 0 to 2.
5. Patients whose survival time is projected to be 12 weeks and longer.
6. Patients aged 18 and older.
7. Patients from whom written consent has been obtained to participate in the study.

Exclusion criteria

1. Patients who received 3 and more regimens of chemotherapy in the past.
2. Patients who received their final dosing of an anticancer drug for systemic administration within 21 days before the first treatment.
3. Patients in whom chronic toxicity exceeding CTC grade 2 has not disappeared after receiving previous anticancer therapy (except patients with alopecia).
4. Patients treated with radiation therapy within 14 days before initial treatment.
5. Patients who have not sufficiently recovered from a previous tumor surgery or other major surgery.
6. Patients complicated with superior vena cava syndrome.
7. Patients in whom new brain metastasis has been diagnosed. In addition, patients who were

previously diagnosed and treated for brain metastasis can be included provided their condition is clinically and radiologically stable 2 months and more before initial treatment.

8. Patients with neurologic symptoms accompanied by spinal cord compression.
9. Patients who have a serious or uncontrolled systemic illness and the assessment of such illness by the principal investigator etc. has exceeded PS2.
10. Patients with significant clinical symptoms or abnormal clinical laboratory values who are not desirable candidates for participation in this study.
11. Patients with a neutrophil count of less than 1500/mm^3 or platelet count of less than 75000/mm^3.
12. Patients whose serum bilirubin is more than 1.25 times the upper normal limit.
13. When hepatic metastasis cannot be confirmed, patients whose ALT or AST levels are more than 2.5 times the upper normal limit. Or, if there is hepatic metastasis, patients whose ALT or AST levels are more than 5 times the upper normal limit.
14. Patients whose serum creatinine level is more than 1.5 times the upper normal limit.
15. Patients judged by the principal investigator etc. to be at risk of transmitting infections such as human immunodeficiency virus (HIV) or hepatitis B from blood or other bodily fluids.
16. Pregnant women or nursing mothers.

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2

Overview of the notifications for self-inspection etc. issued from April 2004 to February 2005

This safety information is an overview of the notifications issued between April 2004 and February 2005 for revisions to be made to the package inserts and self-inspections relating to the safety of medical devices, as post-marketing safety measures for medical devices. The details are carried on the device safety measure notifications at the Pharmaceuticals and Medical Devices Safety Information website (http://www.info.pmda.go.jp/) (in Japanese). Please refer to the self-inspection notifications etc. for each item.

Outlines of notifications on medical devices will also be published as needed in each future edition of Pharmaceuticals and Medical Devices Safety Information.

(1) Self-inspections relating to potential fires etc. from CO_2 absorbent (September 6, 2004)

Although various types of CO_2 absorbents are used in closed circuit anaesthesia machines, there has been overseas report of fire or extreme heat through the use of a certain type of desiccated CO_2 absorbent with the anaesthetic sevoflurane. After requesting an investigation by the manufacturers or importers etc. of anaesthesia machines and CO_2 absorbents, the following was reported. The CO_2 absorbent is an alkaline substance consisting of the main ingredient calcium hydroxide containing approximately 10% to 20% water. The risk of heat generation is not restricted to a certain type of product, but it is possible that there is a common risk associated with using it after desiccation. It is reported that that apart from the risk of fires etc., generation of carbon monoxide and decrease in carbon dioxide absorbing ability are also surmised.

For this reason, a notification has been issued to the manufactures of closed circuit anaesthesiology machine which utilize CO_2 absorbents instructing them to inspect for the presence/absence of the following statements in the "Contraindications" section of the package inserts, and if the existing statements are insufficient, to promptly revise them and to make medical institutions aware of proper methods of use and the aforementioned risks.

"Do not dry out the CO_2 absorbent by opening the package and keeping it or by keeping the inhalational anaesthesia system while it has been supplied with fresh gas (mainly oxygen) etc. (by utilizing the inhalant anaesthetic together with the CO_2 absorbent which has lost its water content, fire, extreme heat, carbon monoxide generation, or decline in CO_2 absorbing ability may occur)."

(2) Self-inspection of PRECAUTIONS for autologous blood collection sets etc. (September 10, 2004)

There was a report that foreign matter entered into the reservoir (for temporary blood storage) from aspiration line (suction tube for the operative field) while the autologous blood collection set was being set up. Results of an investigation revealed that by sealing off the aspiration line and decreasing the pressure of the suction equipment (wall suction inside the hospital, pump inside the device, and external pump at medical institutions) while maintaining a consistent degree of pressure reduction, pressure

reversal occurred at both sides of the autologous blood collection set reservoir (aspiration side and suction equipment side). Thus, the possibility was suggested that foreign matter present in the line of the reservoir suction equipment can become intermixed.

For this reason, it is possible that a wide range of autologous blood collection sets are at risk of the same malfunction. Therefore, a notification has been issued to the relevant manufacturers instructing them to inspect for the presence/absence of the following statements in the "Contraindications" section of the package inserts, and if the existing statements are insufficient, to promptly revise them and to make medical institutions aware of proper methods of use and the aforementioned risks.

1) "Do not reduce the pressure of the suction equipment while the aspiration line (suction tube at the side of the operative field) is sealed off [if suction from the suction equipment (wall suction inside the hospital, pump inside the device, and external pump at medical institutions) stops or decreases while the aspiration line (suction tube at the side of the operative field) is sealed off, it is possible that pressure reversal may occur and foreign matter existing between the reservoir (for temporary blood storage) and the wall suction may become intermixed]."

2) "Always use a regulator (suction control device) between the suction equipment and reservoir. Also, the type of suction line (the tube connecting the regulator to the reservoir) used between the regulator and reservoir should either be one which has been disinfected or a disinfected disposable type. In addition, do not set the regulator to a suction pressure which is less than the pressure prescribed for the suction equipment. [As the pressure reversal phenomenon cannot be completely prevented even by using a regulator, the suction line used between the regulator and reservoir should be one that has been disinfected. Do not set the regulator suction pressure to less than the suction pressure prescribed for the suction equipment, as doing so will inhibit the appropriate use of the regulator]."

3) "Establish the reservoir at higher position relative to the regulator. If the equipment cannot be set up in this manner, loosen the suction line between the regulator and reservoir to a low-lying position between the regulator and reservoir port. [Establishing the reservoir port at a relatively higher position will reduce the pressure reversal phenomenon and decrease the risk of foreign matter becoming intermixed into the reservoir. In addition, this will also prevent condensation resulting from body temperature from entering into the reservoir port]."

4) "Use a single line without branching to connect the suction equipment to the reservoir. [This will prevent the pressure reversal phenomenon due to pressure release from other branch lines]."

(3) Self-inspection of electrosurgical units with bipolar electrodes (September 24, 2004)

Electrosurgical units with bipolar electrodes are being used in haemostatic treatment etc. which commonly use φ 4 mm plugs with fixed pitch and bifurcated φ 4 mm plugs for their bipolar electrode terminals. Of these, it has been confirmed that the φ 4 mm bifurcated cable plugs (hereafter, flying lead) can be accidentally connected to the three-prong output terminal for the monopolar electrode. By unawarely using the equipment in this way (connecting the bipolar electrodes to the monopolar terminal), it has been confirmed that the contacting of the terminals of the bipolar forceps will produce the same effect as when the monopolar output switch is pressed, generating monopolar output at several to 10 times the normal bipolar output. It is possible this may produce serious adverse events for brain surgeons and plastic surgeons etc. who must conduct surgery through detailed bipolar operations. Therefore, a notification has been issued to the relevant manufacturers instructing them to inspect for the presence/absence of the following statements in their package inserts, and if the existing statements are insufficient, to promptly revise them and to make medical institutions aware of proper methods of use and the aforementioned risks.

1) Manufacturers etc. of electrosurgical units etc. for the purpose of haemostasis and coagulation through bipolar output who use the aforementioned flying lead in their products should include the following statement in the "Contraindication" section: "As this product employs a cord exclusively for bipolar terminals, do not connect the cord to a monopolar terminal. (If this cord is accidentally connected to a monopolar output terminal, it is possible that unforeseen electrical output will be generated resulting in serious adverse events)."

2) Manufacturers etc. of electrosurgical units etc. for the purpose of haemostasis and coagulation through bipolar output who utilize the φ 4 mm plug with fixed pitch should include a statement to the following effect in the "Warning" section: "Use only prescribed accessories (φ 4 mm plug with fixed pitch) with this product".

(4) Self-inspection of electrosurgical units used concurrently with puncture needle guides etc. (September 24, 2004)

While cauterization using radio waves and coagulation using microwaves are being conducted, a case has been reported of the insulating membrane on the needle cannula of the electrosurgical unit breaking due to the metallic needle guide used concurrently with the ultrasonic probe to conduct percutaneous administration of this therapy. The breaking of the insulating membrane was resulted in thermal burn to the patient. Results of an investigation suggested the possibility for the insulating membrane to break when inserting the electrosurgical unit into the needle guide etc., and when shifting the needle cannula on the needle guide according to the cauterization site. Therefore, a notification has been issued to the relevant manufacturers instructing them to inspect for the presence/absence of the following statements in their package inserts, and if the existing statements are insufficient, to promptly revise them and to make medical institutions aware of proper methods of use and the aforementioned risks.

1) Manufacturers etc. of electrosurgical units intended for use in cauterization with puncture needles

① A statement to the following effect should be included in the "Warning" section: "When concurrently using a puncture needle guide etc. with this product, handle the needle cannula carefully so as not to damage the insulating membrane on the needle cannula. [when inserting the electrosurgical unit into the puncture needle guide etc. and taking out and putting back the unit along side the puncture needle guide, it is possible to damage the insulating membrane and to scald the tissue in the vicinity of the damaged area]."

② A statement to the following effect should be included in the "Important Precautions" section: "When concurrently using a puncture needle guide etc., with this product, confirm that the electrosurgical unit's needle cannula attachment surface is not damaged and that its operation is smooth, and handle the equipment carefully."

2) Manufacturers etc. of metallic or non-metallic puncture needle guide etc.

① A statement to the following effect should be included in the "Warning" section: "When using the needle cannula of the electrosurgical unit under the guidance of this puncture needle guide, handle the needle cannula carefully so as not to damage the insulating membrane on the needle cannula. [when inserting the needle cannula of the electrosurgical unit into the puncture needle guide and taking out and putting back the cannula along side the puncture needle guide, it is possible to damage the insulating membrane on the cannula and to scald the tissue in the vicinity of the damaged area]."

② A statement to the following effect should be included in the "Important Precautions" section: "Confirm that the needle cannula attachment surface is not damaged and that its operation is smooth before use, and handle the equipment carefully."

(5) Self-inspection of PRECAUTIONS for blood access catheter sets etc. (October 7, 2004)

For a patient with an indwelling blood access catheter set to conduct artificial dialysis, the junction of the diverging tube and the extension tube was reported to be loose. The results of investigation suggested the possibility of serious adverse event occurring such as haemorrhage etc. due to the weakening of the junction bonding strength when the junction of the blood access catheter has been moistened with disinfecting alcohol.

Although this will also depend on adhesive method and manufacturing process, it is possible to assume that the same risk is attendant with a wide range blood access catheter sets currently in use. Therefore, a notification has been issued to the relevant manufacturers of the family of products in question to conduct detailed inspections on the effects of disinfectants etc. containing organic solvents which are surmised to be used in such hospital settings, and if effects are observed, to conduct self-inspection to confirm that the following points are clearly stated in the "Contraindications" section of their package inserts. If these statements are insufficient, they should promptly revise the package inserts and alert medical institutions about the proper use of this product and the aforementioned attendant risks.

1) "Do not allow alcoholic disinfectants such as disinfecting alcohol and hypo solution (a disinfecting and cleaning liquid used for skin washing after the use of an iodine-based disinfectant) to contact the connecting tube junction of this product [allowing alcoholic disinfectants to contact the tube junction may reduce the adhesive strength of the bonding region and cause the tube junction to come apart]."

2) "Do not use organic solvents etc. which are surmised to affect the material of this product [the use of organic solvents may result in shape deformation, degradation, breaking, or peeling of the product]."

(6) Revision of PRECAUTIONS etc. for heat and moisture exchagers (November 26, 2004)

In accordance with PFSB/ELD Notification No. 0315001 issued by the director of the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau, and PFSB/SD Notification No. 0315001 issued by the director of the Safety Division, the Pharmaceutical and Food Safety Bureau dated March 15, 2004, titled "Self-inspection etc. of PRECAUTIONS etc. for heat and moisture condensers", in the event that the power of heat and moisture condenser is left on and the heat and moisture condenser chamber is removed from the artificial respiration circuit so that the unit is directly connected by-passing the heat and moisture condenser chamber, and if after water is supplied from the gas port, the heat and moisture condenser chamber is not reconnected to the artificial respiration circuit immediately water supply, it is possible this may result in serious damage to health such as thermal burn of the respiratory tract. MHLW has requested the following awareness raising activities be conducted on the proper use of the water supply port for the heat and moisture condenser in order to further ensure the safety of patients using this medical device.

○ Manufacturers etc. of heat and moisture condensers at similar risk and manufacturers of artificial respirators which utilize the medical device in question should promptly revise their package inserts as follows (including package inserts of accessories for which simplified statements can be written). In addition, they should alert medical institutions about aforementioned risks.

1) Clearly state in the "Contraindications" section that the gas port should not be used to supply water to the heat and moisture condenser.

   [it is possible doing so may result erroneous connection and burn injury due to erroneous connection, and contamination of the artificial respiration circuit from microbes entering through the gas port].

2) Clearly state in the "Warning" section that when supplying water into the heat and moisture condenser, the water supply port should be used.

3) In addition to the above 1) and 2), provide clear instructions in the "Operation method or usage method" section and "PRECAUTIONS" section as to the proper water supply method through the water supply port, or proper water supply methods by way of medical devices capable of continuous water feed.

(7) Additions to PRECAUTIONS etc. for vacuum blood collection tubes etc. (January 4, 2005)

As raised in PFSB/SD Notification No. 1117001 issued by the director of the Safety Division, the Pharmaceutical and Food Safety Bureau dated November 17, 2003 titled "Self-inspection etc. of PRECAUTIONS etc. for vacuum blood collection tubes", in the event that blood collection using vacuum blood collection tubes is not conducted properly, it is possible that the content and microbes (hereafter, contents etc.) within the blood collection tubes may flow back into the patient's body. Therefore, manufacturers etc. were notified to take appropriate measures to identify the potential risk factors which may result in flow back, and conduct awareness raising activities relating to more detailed methods of using vacuum blood collection tubes etc. Later, as manufacturers of vacuum blood collection tubes, blood collection needles, holders, or products combining these items supply improved disinfected vacuum blood collection tubes, disposable blood collection holders, and rubber sleeved blood collection needles with pressure resistant performance, MHLW notified them to make the following changes to their package inserts etc. and to conduct self-inspections and take appropriate measures.

1st Self-inspection of PRECAUTIONS etc. for disinfected vacuum blood collection tubes

1. When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when product combinations other than the specified product combination are prohibited in the "Contraindications" section of the package inserts for the disinfected vacuum blood collection tubes, these manufacturers should conduct self-inspections to check that the following points have been clearly stated and if these statements are insufficient, they must promptly revise their package inserts. In addition, they should disseminate information to all medical institutions where the relevant products have already been sold, relating to proper blood collection methods and the risks of back flow when using disinfected vacuum blood collection tubes.

(1) The following points should be written in the "Contraindications" section.

① Do not conduct blood collection while the blood collection tubes have not yet returned to room temperature. (there is a risk that the pressure inside the blood collection tubes will change due to the temperature of the blood collection tubes, causing the contents etc. of the blood collection tubes to flow back into the patient's body).

② Do not release or move the pressure on the blood vessel of the patient's arm until the blood collection tube is removed. (there is a risk that when the pressure is released or depending on the position of the patient's arm, venous BP may rapidly drop causing the contents etc. of the blood collection tube to flow back into the patient's body).

③ After the blood begins flowing into the blood collection tube, do not apply force onto the blood collection tube by pushing it into the blood collection holder. (there is a risk that the pressure inside the blood collection tube will change, causing the content etc. of the blood collection tube to flow back into the patient's body).

④ After completing blood collection, do not remove the tourniquet while the blood collection tube is still attached to the blood collection needle. (there is a risk that the change in pressure occurring from

removal of the tourniquet may cause the content etc. of the blood collection tube to flow back into the patient's body).

⑤ Holders should be changed for each patient and disposed of after use. (cross infection may occur if blood adheres to the holder).

⑥ Do not collect blood from an extracorporeal circuit or a central vein. (there is a risk that pressure changes may cause the content etc. of the blood collection tube to flow back into the patient's body).

(2) The following items at the very least should be included in the "Operation Method or Usage Method etc." (including "Dosage and Administration") section, in addition to a detailed and brief entry of other necessary items.

① Prepare blood collection tubes which have returned to room temperature.

② After attaching the tourniquet, disinfect the skin etc.

③ Push the blood collection tube straight and completely into the holder.

④ When the blood flow into the collection tube stops, immediately remove the collection tube from the holder.

⑤ When collecting consecutive samples, replace the blood collection tube while keeping the holder in place.

⑥ After completing blood collection, remove the tourniquet after detaching the blood collection tube from the holder.

(3) The following items should be written to the "Important precautions" in the "PRECAUTIONS" section.

① Confirm that the patient's arm and blood collection tube are always held downward while blood is being collected.

② When collecting blood using a winged needle tube, make sure the position of the blood collection tube does not move up and down.

2. When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when product combinations other than the specified product combination are not prohibited in the "Contraindications" section of the package inserts for the vacuum blood collection tubes, these manufacturers should conduct self-inspections to check that the following points have been clearly stated and if these statements are insufficient, they must promptly revise their package inserts. In addition, they should disseminate information to all medical institutions where the relevant products have already been sold, relating to proper blood collection methods and the risks of back flow when using disinfected vacuum blood collection tubes.

(1) The following items should be written in the "Contraindications" section.

1) When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when different product combinations are prohibited in the "Contraindications" section of the package inserts for these blood collection needles, holders, or their combination products, and when the timing for removing the tourniquet is prescribed in the "Operation Method or Usage Method, etc." (including "Dosage and Administration") section as being after removing the blood collection tube from the holder:

① Do not conduct blood collection while the blood collection tubes have not yet returned to room temperature. (there is a risk that the pressure inside the blood collection tubes will change due to the temperature of the blood collection tubes, causing the contents etc. of the blood collection tubes to flow back into the patient's body).

② Do not release or move the pressure on the blood vessel of the patient's arm until the blood collection tube is removed. (there is a risk that when the pressure is released or depending on the position of the patient's arm, venous BP may rapidly drop causing the contents etc. of the blood collection tube to flow back into the patient's body).

③ After the blood begins flowing into the blood collection tube, do not apply force onto the blood collection tube by pushing it into the blood collection holder. (there is a risk that the pressure inside the blood collection tube will change, causing the content etc. of the blood collection tube to flow back into the patient's body).

④ After completing blood collection, do not remove the tourniquet while the blood collection tube is still attached to the blood collection needle. (there is a risk that the change in pressure occurring from removal of the tourniquet may cause the content etc. of the blood collection tube to flow back into the patient's body).

⑤ Holders should be changed for each patient and disposed of after use. (cross infection may occur if blood adheres to the holder).

⑥ Do not collect blood from an extracorporeal circuit or a central vein. (there is a risk that pressure changes may cause the content etc. of the blood collection tube to flow back into the patient's body).

2) When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when different product combinations for the product are not prohibited in the "Contraindications" section of the package inserts for these blood collection needles, holders, or their combination products, and when the timing for tourniquet removal is prescribed in the "Operation Method or Usage Method, etc." (including "Dosage and Administration") section as being before attaching the first blood collection tube to the holder:

① Include the item ②, followed by items ① to ③ in section 1), followed by the following item ③, concluded by item ⑥ in section 1).

② Do not insert the blood collection tube into the holder while the tourniquet is attached. (If blood collection is started while the tourniquet is attached and the tourniquet is removed after blood collection while the collection tube is still inserted, there is a risk that venous BP will rapidly drop, causing the content etc. of the blood collection tube to flow back into the patient's body).

③ Holders should be changed for each patient (cross infection may occur if blood adheres to the holder).

(2) The following items at the very least should be included in the "Operation Method or Usage Method etc." (including "Dosage and Administration") section, in addition to a detailed and brief entry of other necessary items.

1) When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when different product combinations are prohibited in the "Contraindications" section of the package inserts for these blood collection needles, holders, or their combination products, and when the timing for removing the tourniquet is prescribed in the "Operation Method or Usage Method, etc." (including "Dosage and Administration") section as being after removing the blood collection tube from the holder:

① Prepare a blood collection tube which have returned to room temperature.

② After attaching the tourniquet, disinfect the skin etc.

③ Push the blood collection tube straight and completely into the holder.

④ When the blood flow into the collection tube stops, immediately remove the collection tube from the holder.

⑤ When collecting consecutive samples, replace the blood collection tube while keeping the holder in place.

⑥ After completing blood collection, remove the tourniquet after detaching the blood collection tube from the holder.

2) When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when different product combinations for the product are not prohibited in the "Contraindications" section of the package inserts for these blood collection needles, holders, or their combination products, and when the timing for tourniquet removal is prescribed in the "Operation Method or Usage Method, etc." (including "Dosage and Administration") section as being before attaching the first blood collection tube to the holder:

① Include items ① to ⑤ in section 1), and add the following item ② after including ②.

② After puncturing the vein with the blood collection needle, remove the tourniquet before inserting the blood collection tube.

(3) The following items should be added to the "Important precautions" in the "PRECAUTIONS" section.

① Confirm that the patient's arm and blood collection tube are always held downward while blood is being collected.

② When collecting blood using a winged needle tube, make sure the position of the blood collection tube does not move up and down.

2nd Self-inspection of PRECAUTIONS etc. for the blood collection needles, holders, or their combination products

1. When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when product combinations other than the specified product combination are prohibited in the "Contraindications" section of the package inserts for the blood collection needle, holder, or their combination products, these manufacturers should conduct self-inspections to check that the following points have been clearly stated and if these statements are insufficient, they must promptly revise their package inserts. In addition, they should disseminate information to all medical institutions where the relevant medical devices have already been sold, relating to proper blood collection methods and the risks of back flow when using vacuum blood collection tubes.

(1) The following items should be written in the "Contraindications" section.

① After completing blood collection, do not remove the tourniquet while the blood collection tube is still attached to the blood collection needle (there is a risk that the change in pressure occurring from removal of the tourniquet may cause the content etc. of the blood collection tube to flow back into the patient's body).

② Holders should be changed for each patient and disposed of after use (cross infection may occur if blood adheres to the holder).

(2) The following items at the very least should be included in the "Operation Method or Usage Method etc." (including "Dosage and Administration") section, in addition to detailed and brief entries on other necessary items.

① After attaching the tourniquet, disinfect the skin etc.

② Push the blood collection tube straight and completely into the holder.

③ When the blood flow into the collection tube stops, immediately remove the collection tube from the holder.

④ When collecting consecutive samples, replace the blood collection tube while keeping the holder in place.

⑤ After completing blood collection, remove the tourniquet after detaching the blood collection tube from the holder.

2. When a rubber sleeved blood collection needle with pressure resistant performance and a disposable holder are used for a blood collection needle and a holder respectively, and when product combinations other than the specified product combination are not prohibited in the "Contraindications" section of the package inserts for the blood collection needle, holder, or their combination products, the manufacturers of the products other than such products should conduct self-inspections to check that the following points have been clearly stated and if these statements are insufficient, they must promptly revise their package inserts. In addition, they should disseminate information to all medical institutions where the relevant medical devices have already been sold, relating to proper blood collection methods and the risks of back flow when using vacuum blood collection tubes.

1) The following items should be written in the "Contraindications" section.

① Do not insert the blood collection tube into the holder while the tourniquet is attached (If blood collection is started with the tourniquet is attached and the tourniquet is removed after blood collection while the collection tube is still inserted, there is a risk that venous BP will rapidly drop, causing the content etc. of the blood collection tube to flow back into the patient's body).

② Holders should be changed for each patient (cross infection may occur if blood adheres to the holder).

2) The following items at the very least should be included in the "Operation Method or Usage Method etc." (including "Dosage and Administration") section, in addition to detailed and brief entries on other necessary items.

① After attaching the tourniquet, disinfect the skin etc.

② After puncturing the vein with the blood collection needle, remove the tourniquet before inserting the blood collection tube.

③ Push the blood collection tube straight and completely into the holder.

④ When the blood flow into the collection tube stops, immediately remove the collection tube from the holder.

⑤ When collecting consecutive samples, replace the blood collection tube while keeping the holder in place.

(8) Self-inspection notification relating to the ureteral stent (February 1, 2005)

When removing the ureteral stent which was inserted to promote drainage of urine at times of ureter obstruction or stenosis, there were numerous reports that resistance was felt during the removal of the stent. In all cases, it has been confirmed under X-ray examination that the coil at the end of the ureteral stent was forming a knot within the renal pelvis. The results of investigation suggested that, compared to pigtail-tipped stents, as multi-length ureteral stents which can be used for various ureter lengths form excessively large coils at the stent end, and due to the adherence of calculi on the coil of these large stents, the possibility was suggested that knots would form due to body motion during stent placement or from pulling during stent removal.

In such cases, as there is danger that forced ureteral stent removal may damage the renal pelvis or ureter, confirm the coil formation at the end of the ureteral stent and inspect for the possible formation of a knot. Then, immediately revise the "Warning" section of the package insert by clearly stated the following items etc. In addition, they should alert medical institutions about aforementioned risks.

1) "This product should be used after measuring the length of the patient's ureter and confirming there was no excessive coiling at the stent end. The use of stents with other end configurations should be considered in accordance with related risks. [knot may be formed at the stent end of the renal pelvis side during placement or removal]."

2) "If resistance is felt during removal, the cause of resistance should be confirmed by X-ray etc., then appropriate measures should be taken. [if the stent is forcibly removed, the renal pelvis or ureter may be damaged]."

(9) Safety measures on devices for the self monitoring of blood glucose (among glucose dehydrogenase methods, ones that use pyrrolo-quinoline quinone for a coenzyme) (February 7, 2005)

Regarding safety measures on devices for the self monitoring of blood glucose which employ the glucose dehydrogenase (GDH) method, an Office Memo dated September 29, 2004 was issued requesting revision of the package inserts by adding the following description to the "Warning" section of PRECAUTIONS to alert healthcare providers: "Since blood glucose levels above actual levels can be indicated, this device should not be used on patients taking infusions etc. containing maltose, patients receiving dialysis fluids containing icodextrin, patients undergoing galactose tolerance test or xylose absorption test."

However, even after this notice was issued, there were several case reports which resulted in the onset of hypoglycaemia when this device was used on patients taking infusions containing maltose who were then administered insulin based on these measurements. As these cases were considered to be cases of improper use at medical institutions, the MHLW has notified manufacturers etc. to promptly prepare further countermeasures as we believe that additional safety measures are necessary.

○ Manufacturers etc. of devices for the self monitoring of blood glucose which employ pyrrolo-quinoline quinone for a coenzyme among GDH methods should conduct self-inspection of the package inserts for these devices that they manufacture or import, promptly conduct revisions including the addition of the following item, and alert medical institutions medical institutions utilizing these products about aforementioned risks.

The "Warning" section should be revised as follows:

"Since blood glucose levels above actual levels can be indicated, this device should not be used for the following patients.

Patients taking infusions etc. (as blood glucose levels above actual levels will be indicated for patients taking maltose infusions etc.)

Patients taking dialysis fluid including icodextrin
Patients undergoing galactose tolerance test
Patients undergoing xylose absorption test"

And the following statement should be added:

"As there have been reports of patients taking infusions at medical institutions developing symptoms of hypoglycaemia as a result of administering insulin based on blood glucose measurements taken using this device, in principle this device should only be used for self-monitoring of blood glucose measurements by patients at home."

3

Request for cooperation in Early Post-marketing Phase Vigilance

When new drugs come on to the market, we have only limited information about their safety. The new drug is tested in clinical trials. Since these trials are generally restricted in terms of number of patients, concomitant drugs, complications, age, and other factors, this information has its limitations. However, once a new drug is on the market, as the number of drug users dramatically increase and as the conditions of drug users become much more variegated compared to the patients during the clinical studies, serious adverse reactions etc. which were not made apparent at the clinical studies have been known to occur. In acknowledgment of these unknown characteristics of new drugs, the "early post-marketing phase vigilance" system was implemented from October 2001 to promote particular caution in the use of a new drug during the first 6 months of its marketing, and to strengthen the information gathering system in the event that serious adverse reactions occur.

As criteria for early post-marketing phase vigilance, although the "Good Post-Marketing Surveillance Practice" (GPMSP) had formerly been in effect as the regulations for manufacturers etc., in an effort to strengthen post-marketing safety measures, the "Good Vigilance Practice" (GVP) has been enforced as of April 1, 2005.

As examples of adverse reactions identified at an early stage due to early post-marketing phase vigilance, gefitinib associated with interstitial pneumonia, gatifloxacin associated with hypoglycaemia and hyperglycaemia, and leflunomide associated with interstitial pneumonia can be raised, and revisions were made to their PRECAUTIONS immediately after marketing.

Early post-marketing phase vigilance is a particularly important system in post-marketing safety measures. MHLW hopes that healthcare professionals including physicians, dentists, and pharmacists understand the objective of early post-marketing phase vigilance and ask for your proactive cooperation in reporting such adverse reactions.

Moreover, the list of products under review through early post-marketing phase vigilance as of April 1, 2005 is shown in **Table 1** for reference. The products subject to early post-marketing phase vigilance will be presented in each future edition of the "Pharmaceuticals and Medical Devices Safety Information".

Table 1. List of Products Subject to Early Post-marketing Phase Vigilance (As of April 1, 2005)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Arsenic Trioxide / Trisenox Injection 10 mg	Nippon Shinyaku Co., Ltd.	December 8, 2004
Zoledronic Acid Hydrate / Zometa Injection 4 mg	Nihon Ciba-Geigy K.K.	January 21, 2005
Adefovir Pivoxil / Hepsera Tablets 10	GlaxoSmithKline K.K.	December 8, 2004
Lamivudine / Zefix Tablets 100*[1]	GlaxoSmithKline K.K.	December 8, 2004
Peginterferon Alfa-2b (Genetical recombination) / PegIntron Sterile Powder for Injection 50 μg, 100 μg, and 150 μg	Schering-Plough K.K.	December 8, 2004
Ribavirin / Rebetol Capsules 200 mg*[2]	Schering-Plough K.K.	December 8, 2004
Pamidronate Disodium / Aredia Injection 15 mg and 30 mg*[3]	Nihon Ciba-Geigy K.K.	November 29, 2004
Valganciclovir Hydrochloride / Valixa Tablets 450 mg	Tanabe Seiyaku Co., Ltd.	November 5, 2004
Fosamprenavir Calcium Hydrate / Lexiva Tablets 700	GlaxoSmithKline K.K.	January 7, 2005
Octreotide Acetate / Sandostatin Injection 50 μg and 100 μg	Nihon Ciba-Geigy K.K.	October 22, 2004
Tiotropium Bromide Hydrate / Spiriva Inhalation Capsules 18 μg	Nippon Boehringer Ingelheim Co., Ltd.	December 10, 2004
Beclometasone Dipropionate / Qvar Aerosol 50 and 100	Dainippon Pharmaceutical Co., Ltd.	January 19, 2005
Pralmorelin Hydrochloride / Ghrp Kaken 100 for Injection	Kaken Pharmaceutical Co., Ltd.	February 25, 2005
Aluminum Potassium Sulfate/Tannic Acid / Zione Injection/Lidocaine, Zione Injection	Mitsubishi Pharma Corporation	March 15, 2005
Epinastine Hydrochloride / Alesion Dry Syrup 1%	Nippon Boehringer Ingelheim Co., Ltd.	March 23, 2005
Etanercept (Genetical recombination) / Enbrel 25 mg for s.c. Injection	Wyeth K.K.	March 30, 2005

Note) Subject to additional indication etc.

*1: An additional indication for "in the case of concurrent use with adefovir pivoxil"

*2: An additional indication for "improvement of viraemia in the following chronic hepatitis C cases through concomitant use with peginterferon alfa-2b (Genetical recombination)"

*3: An additional indication for "osteolytic bone metastasis in breast cancer"