Pharmaceuticals and Medical Devices Safety Information

No. 250 September 2008

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

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

Pharmaceuticals and Medical Devices Safety Information

No. 250 September 2008

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

[Outline of Information]

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

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

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

1

Interstitial pneumonia from interferon preparations (preparations with the indication for “improvement of viraemia in chronic hepatitis C”)

	Active ingredient	Brand name (name of Company)
Active Ingredient **Brand Name (name of company)**	Peg-Interferon Alfa-2a (genetical recombination) Interferon Alfa (BALL-1) Interferon Alfa (NAMALWA) Interferon Alfa-2b (genetical recombination) Interferon alfacon-1 (genetical recombination) Interferon Beta Peg-Interferon Alfa-2b (genetical recombination)	Pegasys S.C. Injection 90 μg and 180 μg (Chugai Pharmaceutical Co., Ltd.) OIF 2500000 IU, 5000000 IU, and 10000000 IU (Otsuka Pharmaceutical, Co., Ltd.) Sumiferon 300 and 600, Sumiferon DS 300 and 600 (Dainippon Sumitomo Pharma Co., Ltd.) Intron A S.C. Injection 300, 600, and 1000 (Schering-Plough K.K.) Advaferon S.C. Injection 900, 1200, and 1800 (Astellas Pharma Inc.) IFN β Mochida Injection 1000000, 3000000, and 6000000 units (Mochida Pharmaceutical Co., Ltd.), Feron (Toray Industries, Inc.) Peg-Intron S.C. Injection 50 μg/0.5 mL, 100 μg/0.5 mL, and 150 μg/0.5 mL (Schering-Plough K.K.)
Therapeutic Category	**Biological preparations-Miscellaneous**	
Indications	**Peg-Interferon Alfa-2a (genetical recombination)** 1. Improvement of viraemia in chronic hepatitis C 2. Improvement of viraemia in concomitant use of ribavirin in chronic hepatitis C (1) or (2) (1) Serogroup 1 (patients for genotype I (1a) or II (1b) with high blood HCV-RNA load) (2) Patients who failed interferon monotherapy or who developed reactivation of the disease following interferon monotherapy **Interferon Alfa (BALL-1)** ・Improvement of viraemia in chronic active hepatitis B with positive status for HBe-antigen and DNA polymerase (only for OIF 2500000 IU and 5000000 IU) ・Improvement of viraemia in chronic hepatitis C (excluding the cases with high blood HCV-RNA load) ・Chronic myeloid leukaemia (only for OIF 2500000 IU and 5000000 IU) ・Renal cancer (only for OIF 5000000 IU) **Interferon Alfa (NAMALWA)** ・Renal cancer, multiple myeloma, hairy cell leukaemia ・Chronic myeloid leukaemia ・Improvement of viraemia in chronic active hepatitis B with positive status for HBe-antigen and	

	DNA polymerase ・Improvement of viraemia in chronic hepatitis C (excluding the cases with high blood HCV-RNA load) ・Suppression of progress of clinical symptoms of subacute sclerosing panencephalitis by concomitant use with Inosine Pranobex (only for Sumiferon 300) ・HTLV-I-associated myelopathy (HAM) (only for Sumiferon 300 and Sumiferon DS 300) **Interferon Alfa-2b (genetical recombination)** ・Improvement of viraemia in one of the following chronic hepatitis C 1. In the case of monotherapy with this drug (1) For patients whose blood HCV-RNA load is not high 2. In the case of concomitant therapy with ribavirin (1) For patients whose blood HCV-RNA load is high (2) Patients who failed interferon monotherapy or who developed reactivation of the disease following interferon monotherapy ・Improvement of viraemia in chronic active hepatitis B with positive status for HBe-antigen and DNA polymerase ・Renal cancer, chronic myeloid leukaemia, multiple myeloma **Interferon alfacon-1 (genetical recombination)** ・Improvement of viraemia in chronic hepatitis C **Interferon Beta** ・Malignant melanoma of skin ・Glioblastoma, medulloblastoma, astrocytoma ・Improvement of viraemia in chronic active hepatitis B with positive status for HBe-antigen and DNA polymerase ・Improvement of viraemia in chronic hepatitis C ・Suppression of progress of clinical symptoms of subacute sclerosing panencephalitis by concomitant use with Inosine Pranobex (only for IFN β Mochida) ・Improvement of viraemia in compensated cirrhosis type C (excluding the cases with HCV serogroup 1 and high blood HCV-RNA load) (only for Feron) **Peg-Interferon Alfa-2b (genetical recombination)** Improvement of viraemia in concomitant use of ribavirin in chronic hepatitis C (1) or (2) (1) Patients with high blood HCV-RNA load (2) Patients who failed interferon monotherapy or who developed reactivation of the disease following interferon monotherapy

1. Introduction

The MHLW recently reminded in Pharmaceuticals and Medical Devices Safety Information, No. 245 (March 2008) on overall points of concern regarding adverse reactions etc. resulting from interferon preparations in the treatment of hepatitis viral.

Regarding the development of interstitial pneumonia resulting from interferon preparations, the MHLW has alerted that physicians should provide sufficient explanation to patients about the risk of developing interstitial pneumonia in the "WARNING" section of package inserts, and about the need for sufficient monitoring and measures for interstitial pneumonia in the "Clinically Significant Adverse Reactions" section of package inserts.

On August 8, 2008, the MHLW requested to revise "PRECAUTIONS" of the package inserts to provide additional warning about administering these preparations in patients with a medical history of interstitial pneumonia. The content of these safety measures etc. is described hereinafter.

2. Safety measures relating to interstitial pneumonia

The following **Table** shows the number of reported cases of adverse reactions in the form of interstitial pneumonia from the use of interferon preparations (limited to those preparations used to treat hepatitis C including compensated cirrhosis type C) and estimated number of users (from April 2004 to May 2008) presented by relevant companies. In addition, these reports of adverse reactions were not individually assessed for their causality with the interferon preparations.

Table. The number of adverse reaction reports related to interstitial pneumonia from the use of interferon preparations and estimated number of users (April 2004 to May 2008)

Nonproprietary name <Brand name>	Total [Note 1)] (number of fatal cases)	With a medical history or complications [Note 2)] (number of fatal cases)	Without a medical history or complications (number of fatal cases)	Estimated # of users [Note 3)]
Peg-Interferon Alfa-2a (genetical recombination) <Pegasys>	124 (13)	11 (1)	113 (12)	42600
Interferon Alfa (BALL-1) <OIF>	3 (1)	2 (0)	1 (1)	1300
Interferon Alfa (NAMALWA) <Sumiferon>	2 (0)	0 (0)	2 (0)	8000
Interferon Alfa-2b (genetical recombination) <Intron A>	11 (1)	0 (0)	11 (1)	9000
Interferon alfacon-1 (genetical recombination) <Advaferon>	1 (0)	0 (0)	1 (0)	4000
Interferon Beta <IFN β Mochida>	0 (0)	0 (0)	0 (0)	1100
Interferon Beta <Feron>	4 (1)	1 (0)	3 (1)	8800
Peg-Interferon Alfa-2b (genetical recombination) <Peg-Intron>	78 (6)	1 (0)	77 (6)	94000

Note 1): Total number of adverse reactions reported as interstitial lung diseases such as interstitial pneumonia by relevant companies

Note 2): Number of adverse reactions of interstitial lung disease, pulmonary fibrosis, interstitial opacity on chest X-ray, etc. reported as medical histories or complications (including cases of relapse from readministration following discontinuation due to onset of interstitial pneumonia)

Note 3): Number of users treated for hepatitis C including compensated cirrhosis type C estimated by relevant companies

An expert review on the status of adverse reaction reports of interstitial pneumonia resulting from treatment with these interferon preparations showed that among patients treated with the Peg-Interferon Alfa-2a (genetical recombination) preparation, there were many adverse reaction reports related to interstitial pneumonia including fatal cases. And as there were many patients with a medical history or complications of interstitial pneumonia, on August 8, 2008, the MHLW has requested relevant companies to revise “PRECAUTIONS” of the package inserts and to add “patients with a history of interstitial pneumonia” to the “Contraindications” sections.

As for other interferon preparations, while there were relatively fewer patients with a medical history or complications of interstitial pneumonia, adverse reactions related to interstitial pneumonia continued to be reported. Therefore, on August 8, 2008, the MHLW has requested relevant companies to revise “PRECAUTIONS”of the package inserts. Therefore, the MHLW instructed them to add “patients with a past history of interstitial pneumonia” to the “Careful Administration” section, and to add wording in the “Important Precautions” sections to the effect that sufficient attention should be given to these patients such as by conducting periodic examinations.

Healthcare providers should take further cares to ensure that they should not treat patients complicated with interstitial pneumonia with interferon preparations, sufficiently confirm patients medical history for interstitial pneumonia, and sufficiently monitor patients for development of interstitial pneumonia during the administrtion of these interferon preparations.

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

Interferon Alfa-2b (genetical recombination)

[Warning]

WARNING

As interstitial pneumonia and suicide attempt may occur associated with administering this drug, particular attention should be paid to "PRECAUTIONS" and the possibility of adverse reactions should be informed adequately to the patient.

[Contraindication]

Patients with a history of interstitial pneumonia

[Adverse Reactions (clinically significant adverse reactions)]

<In the case of monotherapy with this drug>
Interstitial pneumonia, lung infiltration, dyspnoea: Adequately monitor the patient for clinical symptoms of pyrexia, cough, and dyspnoea etc. If any abnormalities are observed, conduct examinations such as a chest X-ray etc. immediately, discontinue administration of this drug, and take appropriate measures such as administration of adrenal corticosteroids. Patients should be instructed to contact a physician immediately if cough or dyspnoea etc. occur. Moreover, as there have been many reports of interstitial pneumonia occurring from the concomitant administration of Shosaikoto, the concomitant should be avoided.

<In the case of concomitant administration with ribavirin>
Interstitial pneumonia, **lung infiltration**, **dyspnoea**: Adequately monitor the patient for clinical symptoms of pyrexia, cough, and dyspnoea etc. If any abnormalities are observed, conduct examinations such as a chest X-ray etc. immediately, discontinue administration of this drug, and take appropriate measures such as administration of adrenal corticosteroids. Patients should be instructed to contact a physician immediately if cough and dyspnoea etc. occur.

Interferon Alfa (BALL-1)
Interferon Alfa (NAMALWA)
Interferon Alfa-2b (genetical recombination)
Interferon alfacon-1 (genetical recombination)
Interferon Beta
Peg-Interferon Alfa-2a (genetical recombination)

[Warning]

WARNING

As interstitial pneumonia and suicide attempt may occur associated with administering this drug, particular attention should be paid to "PRECAUTIONS" and the possibility of adverse reactions should be informed adequately to the patient.

[Careful Administration]

Patients with a history of interstitial pneumonia

[Important Precautions]

Interstitial pneumonia may occur. Patients should be carefully monitored for respiratory symptoms such as pyrexia, cough, and dyspnoea etc. If any abnormalities are observed, examination such as a chest X-ray etc. should be immediately conducted. In particular, when administering the drug to patients with a history of interstitial pneumonia, conduct periodic examinations involving auscultations and chest X-ray etc. and extra caution should be exercised.

[Adverse Reactions (clinically significant adverse reactions)]

In the case of Peg-Interferon Alfa-2b (genetical recombination)
(the wording will differ slightly depending on each product)
Interstitial pneumonia, pulmonary fibrosis, pulmonary oedema: If respiratory symptoms such as pyrexia, cough, and dyspnoea etc. or chest X-ray abnormalities

observed, discontinue administration and take appropriate measures such as administration of adrenal corticosteroids. Patients should be instructed to contact a physician immediately if cough and dyspnoea etc. occur. Moreover, as there have been many reports that interstitial pneumonia occured associated with the concomitant administration of Shosaikoto in the treatment with other interferon alfa preparations, the concomitant administration should be avoided.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Chronic hepatitis C (diabetes mellitus, hypertension)	180 μg (once a week) 11 weeks ↓ 90 μg (once a week) 7 weeks	**Interstitial pneumonia** History of adverse reactions: Interferon Alfa-2b (genetical recombination) + ribivirin (anaemia), Interferon Alfacon-1 (genetical recombination) (interstitial pneumonia) Medical history: interstitial pneumonia HCV Serotype: Group 1 HCV Genotype: 1b HCV-RNA quantification: 3600 KIU/mL (at the start of administration of this drug) Liver biopsy was performed (2 years and 2 months before administration of this drug): tissue diagnosis (F4A3) Previous treatment with interferon preparations: performed [Interferon Alfa-2b (genetical recombination) + ribavirin, Interferon Beta, Interferon Alfacon-1 (genetical recombination)] Smoking history: former smoker (for 38 years) History of using Kampo medicine, health foods etc.: none Approx. 3 years and 8 months before administration: Treatment with an interferon preparation was started. 1 year and 10 months before administration: Administration of 18000000 IU of Interferon Alfacon-1 (genetical recombination) 3 times a week (for approximately 5 months) was started. 1 year and 6 to 7 months before administration: The patient complained of cough and dyspnoea on exertion during the administration of Interferon alfacon-1 (genetical recombination). This is surmised to be the onset of interstitial pneumonia. The patient's condition was seemed not serious as far as could be judged by chest X-ray images. Only the use of interferon was discontinued under no hospitalization. The symptoms improved without administration of steroids etc. 1 year and 5 months before administration: KL-6 was 2766 U/mL. Thereafter fluctuating at the 1000 U/mL level. Chest X-ray findings: slight shadow was confirmed at the lower lung field. 7 months before administration: KL-6 was 1483 U/mL. 5 days before administration: KL-6 was 1203 U/mL. On day 1 of administration: Administration of this drug [Peg-Interferon Alfa-2a (genetical recombination)] at 180 μg/week was started to treat chronic hepatitis C.

				[Findings at the start of administration of this drug] ・Symptoms: no abnormalities [however, it is possible there was persisted dyspnoea (respiratory discomfort) following onset of interstitial pneumonia due to Interferon Alfacon-1 (genetical recombination)] ・Auscultation, chest X-ray, chest CT findings: not performed ・SP-D, CA19-9, and other respiratory function tests: not performed 85 days after administration: As the patient complained of discomfort due to development of general malaise and dyspnoea on exertion, dosage of this drug was reduced (90 μg/week). There were no abnormal findings etc on chest X-ray and CT. 136 days after administration (day of discontinuation): Final administration of this drug was performed. 10 days after discontinuation: The patient was transported to hospital by ambulance due to onset of interstitial pneumonia. She had dry cough and dyspnoea. The patient was referred to an internist. ・Auscultation: velcro rale ・Chest X-ray findings: abnormalities (diffuse interstitial shadows in both lung fields) ・Chest CT findings: abnormalities (diffuse ground-glass opacity in both lung fields, peripheral reticular opacity) IV drip infusion of minocycline hydrochloride at 200 mg/day was started (for 5 days). 11 days after discontinuation: KL-6 was 4511 U/mL. IV drip infusion of methylprednisolone sodium succinate at 500 mg/day was started for interstitial pneumonia (for 2 days). IV drip infusion of panipenem/betamipron at 1.0 g/day was started (for 8 days). 14 days after discontinuation: Oral administration of prednisolone (60 mg/nonuniform administration) was started for interstitial pneumonia (for 5 days). 18 days after discontinuation: KL-6 was 6975 U/mL. Administration of clarithromycin at 400 mg/day was started (for 2 days). 19 days after discontinuation: Oral administration of prednisolone (50 mg/nonuniform administration) was conducted for interstitial pneumonia. 20 days after discontinuation: IV drip infusion of methylprednisolone sodium succinate at 1000 mg/day was started for interstitial pneumonia (for 3 days). IV drip infusion of 1000 mg/day of pazufloxacin mesilate was started. Chest X-ray images showed aggravation of diffuse shadows in both lung fields. IVH was implemented. 21 days after discontinuation: IV drip infusion of micafungin sodium at 150 mg/day was started. 23 days after discontinuation: IV drip infusion of prednisolone sodium succinate at 60 mg/day was conducted for interstitial pneumonia (for 3 days). 24 days after discontinuation: Pneumonia developed. It is surmised that symptoms were complicated by pneumonia by mycosis, pneumocystis carinii infection or bacterial infection in interstitial pneumonia.

				SpO_2 was dropped to 70% level. CRP increased, and pyrexia developed. Chest X-ray images showed pneumonia interstitial diffuse shadow and infiltrative shadow in the lower left lung field. Descending aorta silhouette sign was (+), MRSA: 2+. IV drip infusion of ceftazidime hydrate at 2 g was started. The patient was put on artificial respirator (maintained at FiO_2 1.0). 25 days after discontinuation: β-D-glucan was 331.2 pg/mL. Streptococcus oralis was positive. 26 days after discontinuation: The patient died.
	Concomitant medications: ursodeoxycholic acid, teprenone, magnesium oxide, glibenclamide, telmisartan, theophylline			

Clinical Laboratory Values

	1 year and 5 months before admin.	7 months before admin.	5 days before admin.	On day 1 of admin.	85 days after admin.	136 days after admin. (day of discontinuation)	7 days after discontinuation	10 days after discontinuation
KL-6 (U/mL)	2766	1483	1203	—	—	—	—	—
LDH (IU/L)	—	—	—	285	402	399	494	517
CRP (mg/dL)	—	—	—	0.32	0.17	0.49	1.05	2.82
WBC (/mm^3)	—	—	—	6200	3700	3700	5200	5200

LDH: Lactate Dehydrogenase WBC: White Blood Cell
CRP: C-Reactive Protein

	11 days after discontinuation	18 days after discontinuation	20 days after discontinuation	21 days after discontinuation	22 days after discontinuation	24 days after discontinuation	25 days after discontinuation
KL-6 (U/mL)	4511	6975	—	—	—	—	—
LDH (IU/L)	—	594	237	1038	879	792	882
CRP (mg/dL)	—	2.62	1.20	1.50	1.22	2.37	5.82
WBC (/mm^3)	—	8400	25300	16800	13600	21200	18200

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 70s	Chronic hepatitis C (abnormal hepatic function, hypothyroidism, muscle spasm, interstitial pneumonia)	90 μg (once a week) 25 weeks	**Interstitial pneumonia** Medical history: interstitial pneumonia, bronchiectasis, abnormal hepatic function HCV Genotype: 1b Liver biopsy was performed (1 day before administration): tissue diagnosis (F3A2) Pretreatment: hepatoprotector (administered for 16 years until 4 days before administration of this drug), no history of interferon treatment. Smoking history: none History of using Kampo medicine, health foods etc.: none 1 year and 4 months before administration: There were no abnormal findings on X-ray. On day 1 of administration: Administration of this drug [Peg-Interferon Alfa-2a (genetical recombination)] at 90 μg/week was started for chronic hepatitis C. [Findings at the start of administration of this drug] ・Symptoms: not performed ・Auscultation: not performed ・Chest X-ray: performed (date of implementation: on the month of starting administration) ・Findings: abnormalities found, mild (interstitial pneumonia) ・Chest CT: not performed ・KL-6, SP-D, CA19-9: not performed ・Other respiratory function tests: not performed 7 days after administration: The second administration of this drug was performed. Neutropenia (no serious) suddenly developed. 14 days after administration: Neutropenia was in remission. This drug was administered three times. 35 days after administration: Administration of this drug was started at another hospital. Follow-up was conducted at this hospital once a month. Weight was 64.5 kg. Weight increased by 1 kg every day from around the time of the fourth administration. The patient experienced leg cramps. Spironolactone at 50 mg, furosemide at 20 mg, and Shakuyakukanzoto at 7.5 g were administered. Approx. 60 days after administration: Interstitial pneumonia worsened. Approx. 70 days after administration: Pulse rate increased when climbing up and down stairs. There was mild cough. Weight gained and hair loss developed (no serious). 84 days after administration: Eczema (whole body) and generalised oedema particularly on both legs developed (no serious). After 175 days of administration (day of discontinuation): Anasarca, weight gained, and generalised eczema became pronounced, legs became swollen, and walking became difficult. Administration of this drug was discontinued. Medication was switched to injection of hepatoprotector.

				Approx. 1 month after discontinuation: Sputum, cough, and hair loss developed. Approx. 2 months after discontinuation: Cough (morning and evening), and white sputum developed. There was mild cough, white sputum increased, and slight dyspnoea. There was no pyrexia. Approx. 3 months after discontinuation: Sputum, cough, and hair loss intensified. 99 days after discontinuation: Interstitial pneumonia was confirmed from chest X-ray and chest CT. Symptoms: dry cough (mild), and mild tachycardia. [Findings at the onset of interstitial pneumonia] ・Symptoms: observed (dry cough, sputum, dyspnoea, and fatiguability) ・Auscultation: velcro rale ・Chest X-ray, chest CT: abnormal findings (interstitial pneumonia) ・KL-6, SP-D, CA19-9, and other respiratory function tests: not performed. 109 days after discontinuation: The patient recovered from eczema (whole body). 119 days after discontinuation: The patient was hospitalized to the respiratory department of this hospital and underwent detailed examination. The patient was orally administered erythromycin and carbocisteine to treat bronchiectasis. Sputum decreased through practice at coughing up sputum. Dyspnoea improved. 129 days after discontinuation: Hair loss improved. The patient did not yet recuperate from generalized oedema, particularly both legs, and from weight increase. 131 days after discontinuation: As aggravation of symptoms was seen, steroid treatment was recommended. However, the patient did not consent and her condition was monitored over time. The patient was discharged from the hospital. 167 days after discontinuation: Aggravation of interstitial pneumonia became less severe.
	Concomitant medications: ursodeoxycholic acid, levothyroxine sodium, shakuyakukanzoto			

Clinical Laboratory Values

	1 day before administration	28 days after administration	38 days after administration	56 days after administration	112 days after administration	140 days after administration
KL-6 (U/mL)	—	—	—	—	—	—
LDH (IU/L)	264	286	318	392	298	255
CRP (mg/dL)	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25
WBC (/mm^3)	2300	1900	1500	2000	1900	2100

LDH: Lactate Dehydrogenase WBC: White Blood Cell
CRP: C-Reactive Protein

	168 days after administration	175 days after administration (day of discontinuation)	22 days after discontinuation	99 days after discontinuation	112 days after discontinuation	150 days after discontinuation
KL-6 (U/mL)	—	—	—	—	3030	—
LDH (IU/L)	267	—	298	—	253	286
CRP (mg/dL)	<0.25	—	<0.25	—	<0.25	<0.25
WBC (/mm^3)	1900	2700	2000	3200	3900	3400

2

Revision of PRECAUTIONS

(No. 200)

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated August 8, 2008 [excluding those presented in "1. Interstitial pneumonia from interferon preparations (preparations with the indication for "improvement of viraemia in chronic hepatitis C")" of this Bulletin].

<Antineoplastics-Miscellaneous >

1 Gefitinib

[Brand Name] Iressa Tablets 250
(AstraZeneca K.K.)

[Other Precautions] The phase III post-marketing clinical study comparing survival times for this drug (250 mg/day) versus docetaxel (administration of 60 mg/m^2) was conducted in progressive/metastatic (stage IIIB/stage IV) or postoperative recurrent non-small cell lung cancer patients with a history of treatment with 1 or 2 domestic chemotherapy regimens. Median overall survival was 11.5 months for the Iressa group versus 14.0 months for the docetaxel group (hazard ratio: 1.12, 95.24% confidence interval: 0.89–1.40). Noninferiority of this drug in relation to docetaxel in terms of overall survival time was not demonstrated.

Refer to the reference materials

<Common cold drugs >

2 Salicylamide/Acetaminophen/Anhydrous Caffeine/Promethazine Methylenedisalicylate

[Brand Name] PL Granules, PL Granules for Children
(Shionogi & Co., Ltd), and others

[Adverse Reactions (clinically significant adverse reactions)]

Aplastic anaemia, pancytopaenia, agranulocytosis, haemolytic anaemia, platelets decreased: Aplastic anaemia, pancytopaenia, agranulocytosis, haemolytic anaemia, and platelets decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

Hepatitis fulminant, hepatic function disorder, jaundice: Hepatitis fulminant, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken

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< Antihypertensives >

3 Alacepril, Imidapril Hydrochloride, Captopril, Quinapril Hydrochloride, Cilazapril, Temocapril Hydrochloride, Delapril Hydrochloride, Trandolapril, Pelindopril Erbumine, Lisinopril

[Brand Name] CETAPRIL Tablets 12.5mg, 25 mg, and 50 mg (Dainippon Sumitomo Pharma Co., Ltd.), and others
TANATRIL Tablets 2.5, 5, and 10 (Mitsubishi Tanabe Pharma Corporation), and others

	CAPTORIL Fine Granules, CAPTORIL Tablets 12.5 mg and 25 mg, CAPTORIL-R (Daiichi Sankyo Company, Limited), and others Conan Tablets 5 mg, 10 mg, and 20 mg (Mitsubishi Tanabe Pharma Corporation), and others INHIBACE Tablets 0.25, 0.5, and 1 (Chugai Pharmaceutical Co., Ltd.), and others ACECOL Tablets 1 mg, 2 mg, and 4 mg (Daiichi Sankyo Company, Limited) ADECUT 7.5 mg, 15 mg, and 30 mg Tablets (Takeda Pharmaceutical Company Limited), and others Odric Tablets 0.5 mg and 1mg (Nippon Shinyaku Co., Ltd.), Preran 0.5 mg and 1 mg Tablets (Sanofi-Aventis K.K.), and others COVERSYL Tablets 2 mg and 4 mg (Kyowa Hakko Kogyo Co., Ltd.), and others ZESTRIL Tablets 5, 10, and 20 (AstraZeneca K.K.), Longes Tablets 5 mg, 10 mg and 20 mg (Shionogi & Co., Ltd.), and others
[Use in Pregnant, Parturient And Nursing Women]	This drug should not be administrated to pregnant women or to women who may be pregnant. If pregnancy is confirmed during administration, immediately discontinue administration.

< Antihypertensives >

4 Enalapril Maleate

[Brand Name]	Renivace Tablets 2.5 mg, 5 mg, and 10 mg (Banyu Pharmaceutical Co., Ltd.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Syndrome inappropriate ADH (SIADH):** Syndrome inappropriate ADH (SIADH) with hyponatraemia, blood hyposmosis, increased sodium excretion into the urine, hypersthenuria, convulsions, and consciousness disturbed may occur. In such cases, administration should be discontinued and appropriate measures such as restricting fluid intake etc. should be taken.
[Use in Pregnant, Parturient And Nursing Women]	This drug should not be administrated to pregnant women or to women who may be pregnant. If pregnancy is confirmed during administration, immediately discontinue administration.

< Antihypertensives >

5 Benazepril Hydrochloride

[Brand Name]	Cibacen Tablets 2.5 mg, 5 mg and 10mg (Novartis Pharma K.K.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatitis, hepatic function disorder, jaundice**: Hepatitis, hepatic function disorder, and jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Agranulocytosis, neutropenia**: Agranulocytosis and neutropenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. It has been reported that these conditions more readily occur in patients with renal disorder, patients with an autoimmune disease (particularly systemic lupus erythematosus), or patients taking an immunosuppressant who were taking an ACE inhibitor. **Pancreatitis**: Pancreatitis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
[Use in Pregnant, Parturient And Nursing Women]	This drug should not be administrated to pregnant women or to women who may be pregnant. If pregnancy is confirmed during administration, immediately discontinue administration.

<Epidermides-Miscellaneous >

6 Tacrolimus Hydrate (ointment for adults)

[Brand Name] Protopic Ointment 0.1%
(Astellas Pharma Inc.)

[Warning]

WARNING

In a carcinogenicity study in mice, increased incidence of lymphoma due to persistently higher blood concentrations of tacrolimus was observed. Although a causal relationship has not been established, it has been reported that lymphoma and skin cancer developed in patients treated with this drug. Physicians should explain these information to patients and confirm their understanding before prescribing this drug.

<Epidermides-Miscellaneous >

7 Tacrolimus Hydrate (ointment for pediatric)

[Brand Name] Protopic Ointment 0.03% for pediatric
(Astellas Pharma Inc.)

[Warning]

WARNING

In a carcinogenicity study in mice, increased incidence of lymphoma due to persistently higher blood concentrations of tacrolimus was observed. Although a causal relationship has not been established, it has been reported that lymphoma and skin cancer developed in patients treated with this drug. Physicians should explain these information to patients and confirm their understanding before prescribing this drug.

<Acting mainly on gram-positive bacteria and gram-negative bacteria>

8 Amoxicillin Hydrate

[Brand Name] Sawacillin Fine Granules 10%, Sawacillin Tablets 250 mg, Sawacillin Capsules 250 mg (Astellas Pharma Inc.), PASETOCIN Fine Granules 10%, PASETOCIN Tablets 50 and 250, PASETOCIN Capsules 125 and 250 (Kyowa Hakko Kogyo Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), and acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored. If abnormalities such as pyrexia, headache, arthralgia, erythaema and blister of the skin and membranes, pustule, and skin tightness, burning sensation, and pain of skin, etc. are observed, administration should be discontinued and appropriate measures should be taken.

<Antibiotics-Miscellaneous>

9 Lansoprazole/Amoxicillin Hydrate/Clarithromycin

[Brand Name] LANSAP 400 and 800
(Takeda Pharmaceutical Company Limited)

[Adverse Reactions (clinically significant adverse reactions)] Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), and acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored. If abnormalities such as pyrexia, headache, arthralgia, erythaema and blister of the skin and membranes, pustule, and tension, burning sensation, and pain of skin, etc. are observed, administration should be discontinued and appropriate measures should be taken.

10 <Chemotherapeutics-Synthetic antibacterials>

Garenoxacin Mesilate Hydrate

[Brand Name]	Geninax Tablets 200 mg (Toyama Chemical Co.,Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Bradycardia, sinus arrest, atrioventricular block**: Bradycardia, sinus arrest, and atrioventricular block (initial symptoms: queasy, dizziness, syncope etc.) may occur. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Agranulocytosis:** Agranulocytosis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feeling of weakness, CK (CPK) increased, and blood myoglobin increased and urine myoglobin increased, with rapid worsening of renal function may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken .

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List of products subject to Early Post-marketing Phase Vigilance

(As of September 1, 2008)

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

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

*1: An additional indication for “rhinitis allergic”
*2: Additional indications for “rheumatoid arthritis (including prevention for structural damage of joints), polyarticular-course juvenile idiopathic arthritis, and systemic-onset juvenile idiopathic arthritis”
*3: An additional indication for “prophylaxis of vein thromboembolism in patients undergoing abdominal surgery who are at risk for venous thromboembolism”
*4: An additional indication for “prophylaxis of thrombosis in patients with heparin-induced thrombocytopenia (HIT) type II”
*5: An additional indication for “reducing blood phenylalanine levels in patients with hyperphenylalaninemia (tetrahydrobiopterin-responsive hyperphenylalaninemia) due to tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency”
*6: An additional indication for “Paget disease of bone”

Reference Material

Results of the Gefitinib domestic phase III study etc. and opinions on Gefitinib use etc.

The result of review on"Results of the Gefitinib domestic phase III study etc. and opinions on Gefitinib use etc."in the Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council (held on August 1, 2008) is presented. Please refer to the reference materials from the Subcommittee on Drug Safety available on the MHLW website (http://www.mhlw.go.jp/) in Japanese, as well.

August 1, 2008

Subcommittee on Drug Safety
Committee on Drug Safety
Pharmaceutical Affairs and Food Sanitation Council

Results of the Gefitinib domestic phase III study etc. and opinions on Gefitinib use etc.

○ **On February 1, 2007, this subcommittee reviewed the results of a "multicenter, unblind, randomized phase III post-marketing clinical study that compared Gefitinib versus Docetaxel on overall survival in patients with advanced or metastatic (stage III B or stage IV) non-small cell lung cancer (NSCLC) who failed 1 or 2 chemotherapy regimens" (hereafter, "the domestic phase III study") which were submitted by pharmaceutical companies.**

○ **Considering that the frequencies of adverse reaction associated with the use of Gefitinib are at a comparable level to those adverse reactions outlined in the latest package inserts etc., we deemed it appropriate that current safety measures mentioned in package inserts, such as sufficiently monitoring for the onset of serious adverse reactions such as interstitial pneumonia etc. under hospitalization at least for 4 weeks after initiating administration or under similar conditions be conducted, and that this drug be used only by physicians possessing sufficient experience in administering lung cancer chemotherapy.**

○ **To assess the clinical usefulness of Gefitinib with respect to its efficacy, it was deemed necessary to confirm the results suggesting that the Docetaxel group was superior to the Gefitinib group in terms of survival rate during the initial stage of administration etc., as well as to conduct further detailed analysis of patient background, influence of post-treatment, and unprocessed data.**

○ **Today, this subcommittee reviewed the results of analysis the above details regarding the domestic phase III study submitted by pharmaceutical companies. The subcommittee also reviewed the results of the "multicenter, unblind, randomized phase III study that compared Gefitinib and Docetaxel in patients with locally advanced or metastatic non-small cell lung cancer pre-treated with platinum-based chemotherapy" (hereafter, "INTEREST* Study").**
***INTEREST: Iressa NSCLC Trial Evaluation Response and Survival against Taxotere Trial**

○ **Results of the domestic phase III study and the INTEREST Study, and opinions on Gefitinib use etc. are provided below.**

I. Results of the domestic phase III study and the INTEREST Study

1. The domestic phase III study

○ **The noninferiority of the Gefitinib group compared to the Docetaxel group in terms of overall survival time was not demonstrated [hazard ratio= 1.12 (95.24% confidence interval 0.89–1.40)]. While post-treatment might have had some influence on overall survival time, it is judged that this influence could not be accurately assessed.**

○ **When each subgroup was compared in terms of overall survival time which is a primary endpoint, there were no subgroups which showed that the efficacy of Gefitinib was clearly higher compared to Docetaxel. Moreover, with respect to EGFR gene mutations, as there were very few cases of death, it was difficult to assess overall survival time.**

○ **Based on the above results etc., we judged it was not necessary to change the investigative results of the Subcommittee on Drug Safety conducted on February 1, 2007 [there is, generally, no evidence for willingly choosing to administer Gefitinib over Docetaxel to treat patients with inoperable or recurrent non-small cell lung cancer with a medical history of 1 or 2 regimens of chemotherapy (including at least 1 regimen of platinum preparation)].**

2. The INTEREST Study

○ **The INTEREST Study(note1) was conducted with participation by 24 countries(note 2) which included Asian countries.**

(note 1): Number of randomly allocated cases to the INTEREST Study: 1466 cases; number of randomly allocated cases to the domestic phase III study: 490 cases

(note 2): Japan did not participate. 21% of registered cases were from Asian countries (China, Hong Kong, Indonesia, Malaysia, the Philippines, and Thailand).

○ **The noninferiority of the Gefitinib group compared to the Docetaxel group in terms of overall survival time was demonstrated [hazard ratio = 1.020 (96% confidence interval 0.905–1.150)]. As well, the hazard ratio was similar for Asians (1.04) and non-Asians (1.01).**

II. Gefitinib use etc.

○ **Based on the results of the domestic phase III study and the INTEREST Study, by continuing current safety measures such as close monitoring of the onset of serious adverse reactions such as interstitial pneumonia etc. under hospitalization for at least 4 weeks after the start of administration or under similar conditions, this drug is clinically useful for the treatment of inoperable or recurrent non-small cell lung cancer.**

○ **Based on the results of the above I.1. the domestic phase III study, and in conformity with the review by the Subcommittee on Drug Safety conducted on February 1, 2007, it is appropriate that pharmaceutical companies be instructed to inform medical and healthcare providers that they should fully explain to patients the results of the domestic phase III study and how insufficient evidence exists to recommend the use of Gefitinib over Docetaxel generally to treat patients with inoperable or recurrent non-small cell lung cancer with a medical history of 1 or 2 regimens of chemotherapy (including at least 1 regimen of platinum preparation).**

For the purpose of providing the above information, it is recommended that the results of the domestic phase III study (overview) be outlined in the "Other Precautions" section in package inserts.

○ **It is recommended that the MHLW continues to collect information relating to the efficacy and safety of this drug domestically and from abroad and to take necessary measures.**