Pharmaceuticals and Medical Devices Safety Information

No. 245 March 2008

Table of Contents

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

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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. 245 March 2008

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

[Outline of Information]

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

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

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

1

Treatment of hepatitis viral with interferon products

	Active ingredient	Brand name (name of Company)
Active Ingredient **Brand Name (name of company)**	Interferon alfacon-1 (genetical recombination)	Advaferon S.C. Injection 900, 1200, and 1800 (Astellas Pharma Inc.)
	Interferon Alfa (BALL-1)	OIF 2500000 IU, 5000000 IU, and 10000000 IU (Otsuka Pharmaceutical, Co., Ltd.)
	Interferon Alfa (NAMALWA)	Sumiferon 300 and 600, Sumiferon DS 300 and DS600 (Dainippon Sumitomo Pharma Co., Ltd.)
	Interferon Alfa-2b (genetical recombination)	Intron A S.C. Injection 300, 600, and 1000 (Schering-Plough K.K.)
	Interferon Beta	IFN β Mochida Injection 1000000 units, 3000000 units, and 6000000 units (Mochida Pharmaceutical Co., Ltd.), Feron (Toray Industries, Inc.)
	Peg-Interferon Alfa-2a (genetical recombination)	Pegasys S.C. Injection 90 μg and 180 μg (Chugai Pharmaceutical Co., Ltd.)
	Peg-Interferon Alfa-2b (genetical recombination)	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	**Interferon alfacon-1 (genetical recombination)** ・ Improvement of viraemia in chronic hepatitis C **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)** (Sumiferon 300 and 600, Sumiferon DS300 and DS600) ・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) (Sumiferon 300) ・ Suppression of progress of clinical symptoms of subacute sclerosing panencephalitis by concomitant use with Inosine Pranobex (Sumiferon 300 and Sumiferon DS 300) ・HTLV-I-associated myelopathy (HAM) **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 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-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 **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

As provision of medical subsidies for interferon treatment of hepatitis viral will begin in April of this year at the earliest, the number of patients with hepatitis viral who receive this treatment is expected to increase. This section presents types and incidence of the adverse reactions to remind of alert about the treatment of hepatitis viral using the products.

2. Treatment of hepatitis viral with interferon products

Interferon products used for the treatment for viral hepatitis B or viral hepatitis C include Interferon Alfa, Interferon Beta, consensus interferon (Alfacon), Peg-Interferon. Each drug has different antiviral effects, indications, and tendency of adverse reactions. Physicians choose appropriate treatment method according to the patient's physical conditions and symptoms (type or load of virus). In some cases, patients with hepatitis C are treated with combination therapy using some of Interferon Alfa products or Peg-Interferon products plus an antiviral drug (ribavirin).

There have been reports of moderate to severe adverse reactions which require reduction or discontinuation of the product in the initial period of treatment with interferon products. As a general rule, patients with higher risk of developing serious adverse reactions, for example, are hospitalized for at least for 2 weeks from the start of treatment.

Following therapeutic guidelines have been established for chronic hepatitis.

"Guideline on Chronic Hepatitis Examination and Treatment"
(http://www.jsh.or.jp/medical/gudelines/index.html: The Japan Society of Hepatology)

"Guideline on Medical System for Hepatic Disorder after Hepatitis Test in Each Prefecture in Japan"
(Report of the National Hepatitis C Examination and Treatment Society)
(http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/03.html#top)

Health and Labour Sciences Research Grants, The Research Project of Emergency Strategy for the Conquest of Hepatitis, etc. "Clinical Research for Standardizing Treatment for Hepatitis B or Hepatitis C viruses-infected patients" (Fiscal Year 2005 General Partial Research Report)
(http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do)

3. PRECAUTIONS

Administration of interferon products may cause serious adverse reactions such as interstitial pneumonia, suicide attempt, etc. Physicians should be encouraged to be fully aware of the contents of "PRECAUTIONS" such as "Warning", "Contraindications", "Important Precautions", "Clinically

Significant Adverse Reactions" in the package inserts of these products. Major descriptions are shown below.

"PRECAUTIONS" in the package insert of each product is available on "Label Information on prescription drug products marketed in Japan" of the pharmaceuticals and medical devices information website (PMDInfoWeb) (http://www.info.pmda.go.jp/) by the Pharmaceuticals and Medical Devices Agency.

(1) Warning

Administration of interferon products may cause serious adverse reactions such as interstitial pneumonia, suicide attempt. Physicians should be encouraged to be fully aware of the contents of "PRECAUTIONS", and to adequately advise patients of the possible occurrence of these adverse reactions.

(2) Contraindications

This product is contraindicated in patients:

① with taking shosaikoto.
Interstitial pneumonia may develop.

② with autoimmune hepatitis.
Autoimmune hepatitis may aggravate.

③ with a history of hypersensitivity to interferon products.

④ with a history of hypersensitivity to biological preparations such as vaccines.

⑤ who are low birth weight baby, neonates, infants, pediatric under 3 years old (for Peg-Interferon Alfa-2a, Pegasys®).
Deaths of neonates and infants related to excessive exposure to benzyl alcohol in this product have been reported.

⑥ with a history of hypersensitivity to bovine-derived materials (for Interferon Beta, Feron® and IFN β Mochida).

(3) Clinically significant adverse reactions

Serious adverse reactions that may occur during the treatment with interferon products include interstitial pneumonia, suicide attempt, depression, bleeding tendency due to platelet count decreased, cerebral haemorrhage. These events should be addressed by medical intervention such as hospitalization, and may result in fatal outcome in some cases. In particular, the risk of interstitial pneumonia and suicide attempt is described in the Warning section of the package inserts of all interferon products to alert prescribers and patients.

Other clinically significant adverse reactions include autoimmune phenomena (thyroid function abnormal, autoimmune hepatitis, haemolytic anaemia, colitis ulcerative, rheumatoid arthritis, diabetes mellitus insulin-dependent, SLE, myasthenia gravis, aggravation or development of polymyositis), diabetes mellitus, thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), serious liver disorder, serious renal disorder (renal failure acute, nephrotic syndrome, etc.), shock, serious heart disorder (cardiac failure, angina pectoris, myocardial infarction, atrioventricular block complete, ventricular tachycardia, cardiomyopathy, endocarditis, etc.), serious central nervous system/psychoneurotic disorder (consciousness disturbed, confusion, excitement, orientation disturbed, syncope, convulsion, delirium, manic state, hallucination/delusion, dementia-like symptom, etc.), retinopathy, sepsis, cerebral infarction, gastrointestinal haemorrhages, peptic ulcer, colitis ischaemic, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, psoriasis, rhabdomyolysis, dyspnoea, pulmonary fibrosis, pulmonary oedema, arrhythmia, aplastic anaemia, pancytopenia, agranulocytosis, leukopenia, anaemia and serious skin ulcer, etc.

(4) Common adverse reaction

Various adverse reactions are observed during the treatment with interferon products. Examples of common adverse reactions are flu like symptoms (pyrexia, headache, malaise, arthralgia, etc.), blood test abnormal (haemoglobin decreased, platelet count decreased, leucopenia, etc.), alopecia, itching, abdominal pain, appetite impaired, diarrhoea, nausea/vomiting, injection site inflammation and itching,

and sleep loss. The incidence of major adverse reaction is shown in <**Reference**>.
It is known that the types of adverse reactions are different according to the duration from the initiation of treatment. Since most of these adverse reactions are transient, reduction or discontinuation of administration can usually relieve these events.

① Initial period of administration (within 1 week)
Flu like symptoms (pyrexia, headache, malaise, arthralgia, etc.)

② Middle period of administration (at 2 to 12 weeks)
Itching, gingival bleeding/epistaxis (caused by platelet count decreased), anaemia, appetite impaired, abdominal pain, diarrhoea, nausea/vomiting

③ Late period of administration (at 2 to 3 months)
Alopecia (resolved by 5 to 6 months after the end of treatment)

④ Adverse reaction observed throughout treatment period
Injection site inflammation and itching

(5) Adverse reactions in concomitant therapy with ribavirin

Ribavirin, an antiviral agent, is concomitantly used with Peg-Interferon Alfa-2a (genetical recombination), Interferon Alfa-2b (genetical recombination) or Peg-Interferon Alfa-2b (genetical recombination).
Ribavirin may cause significant teratogenicity. Since ribavirin has demonstrated teratogenic and embryocidal effects in animal species, ribavirin is contraindicated in patients who are pregnant or who may be pregnant. Ribavirin has also demonstrated testis/spermatozoa morphology abnormal. Male patients who have femal partners of childbearing potential must be instructed to practice effective contraception.
Adverse reactions in concomitant therapy with ribavirin are usually similar to those with Interferon Alfa products.

4 Closing comments

Healthcare providers should be encouraged to ensure that patients treated with interferon products are closely monitored for early detection and management of the adverse reactions and are given full information on treatment with these products including the initial symptoms of the adverse reactions. Healthcare providers should also be encouraged to utilize “Mannuals for Management of Individual Serious Adverse Drug Reaction” (http://www.info.pmda.go.jp/juutoku_ippan/juutoku_ippan.html) for some serious adverse reactions including interstitial pneumonia (note), and “Drug Guide for Patients” (http://www.info.pmda.go.jp/guide_ippan/guide.html) for interferon products posted on the Pharmaceuticals and Medical Devices Information Website (PMDInfoWeb) when giving information to patients.

(Note) Stevens-Johnson syndrome, toxic epidermal necrolysis, renal failure acute, aplastic anaemia, drug-induced anaemia, bleeding tendency, agranulocytosis, thrombocytopenia, interstitial pneumonia

<Reference> Incidence of major adverse reaction from treatment with each interferon product

(Note) Relatively common adverse reactions are described. Physicians should be encouraged to confirm precaution of each product, since serious adverse reactions with unknown incidence may occur. Physicians should also be encouraged to refer to the interview form of each product regarding details of incidence of each adverse reaction.

● Interferon Alfa (NAMALWA) "Sumiferon®", "Sumiferon®DS"

(Source: extract from Sumiferon®'s interview form (revised in December 2007))

	Chronic active hepatitis B		Chronic hepatitis C				
	Investigation until approval	Drug use-results survey	Investigation until approval	Drug use-results survey *1	Post-marketing clinical study*2	Special drug use-results survey*3	Post-marketing clinical study*4
Number of cases	214	1496	544	3368	275	343	107
Cases of adverse reaction etc.	194	990	471	1628	243	240	105
Incidence of adverse reaction etc.	90.7%	66.2%	86.6%	48.3%	88.4%	70.0%	98.1%
Major adverse reaction							
Pyrexia	79.0%	55.4%	66.4%	29.3%	70.9%	61.2%	73.8%
General malaise			5.1%	3.8%	15.3%	2.6%	5.6%
Malaise	21.5%	7.2%	7.2%	1.7%	0.7%	1.7%	44.9%
Chills	1.9%	1.5%	1.3%	0.1%	2.2%	0.3%	5.6%
Headache	17.8%	5.3%	12.7%	2.3%	16.7%	3.5%	40.2%
Leukopenia	43.5%	22.0%	29.6%	9.4%	22.5%	11.7%	61.7%
Thrombocytopenia	34.6%	20.3%	27.9%	12.9%	24.4%	18.4%	43.0%
Granulocyte count decreased	8.9%	0.8%	1.5%	0.3%	0.7%	0.3%	0.9%
Anaemia		1.0%		0.5%	0.7%	0.3%	
Neutropenia			5.7%	0.2%	5.8%	1.7%	32.7%
Alopecia	11.2%	4.8%	8.8%	7.3%	8.4%	4.7%	27.1%
Rash	2.8%	1.3%	0.9%	0.7%		0.9%	7.5%
Arthralgia	7.9%	2.7%	6.6%	2.5%	15.6%	3.5%	29.9%
Myalgia	5.6%	1.1%	3.5%	1.2%	2.5%	1.2%	12.1%
Queasy	4.7%	2.1%	0.6%	0.6%	3.6%	0.6%	5.6%
Diarrhoea	1.4%	1.2%	0.9%	0.6%		0.6%	15.0%
Appetite impaired	19.2%	4.7%	5.7%	2.0%	0.7%	3.5%	22.4%
AST (GOT) increased	2.8%	2.1%	1.1%	0.2%	1.1%	0.9%	3.7%
ALT (GTP) increased	2.8%	2.3%	1.1%	0.3%	1.1%	2.0%	3.7%

*1: Drug use-results survey for chronic active hepatitis C
*2: Post-marketing clinical study for chronic active hepatitis C
*3: Special drug use-results survey for chronic hepatitis C
*4: Post-marketing clinical study for chronic hepatitis C

● Interferon Alfa (BALL-1) "OIF®"

(Source: interview form of OIF® (revised in December 2006))

	Chronic active hepatitis B		Chronic hepatitis C				
	At the approval	Drug use-results survey	At the approval of chronic active hepatitis*1	Drug use-results survey of chronic active hepatitis*2	Chronic active hepatitis post-marketing clinical study*3	At the approval of chronic persistent hepatitis*4	At the approval of childhood chronic hepatitis C*5
Number of cases	295	515	1109	1298	110	196	38

Cases of adverse reaction etc.	264	397	888	1159	110	181	23
Incidence of adverse reaction etc.	89.5%	77.1%	80.1%	89.3%	100.0%	92.3%	60.5%
Major adverse reaction							
Pyrexia	79.3%	71.8%	63.2%	76.4%	97.3%	79.1%	52.6%
Malaise		0.2%		3.1%	13.6%		
General malaise	14.6%	2.3%	15.5%	9.9%	1.8%	13.3%	
Chills	4.1%	0.2%	0.8%	0.8%	0.9%	0.5%	
Headache	14.9%	3.5%	5.7%	7.6%	10.0%	11.7%	5.3%
Sleep loss		0.6%	0.4%	4.3%	4.5%	1.0%	
Depressed state		0.4%	1.0%	6.2%	5.5%	1.5%	
Anaemia	1.7%	1.0%	0.3%	2.2%	0.9%		
Alopecia	3.7%	1.6%	8.7%	11.9%	7.3%	13.8%	5.3%
Rash	2.0%	0.4%	1.3%	1.8%		2.6%	
Arthralgia	8.1%	3.1%	5.5%	7.8%	15.5%	15.3%	2.6%
Myalgia	0.7%	2.1%	2.9%	3.1%	4.5%	6.1%	2.6%
Queasy		1.0%	1.6%	2.0%	1.8%	2.6%	2.6%
Vomiting	1.0%	0.4%	0.2%	0.5%		1.5%	2.6%
Diarrhoea	3.1%	0.4%	1.8%	2.7%	2.7%	2.6%	
Appetite impaired	13.9%	2.9%	7.3%	7.0%	8.2%	6.1%	2.6%

*1: At the approval of "Improvement of viraemia in chronic active hepatitis C"
*2: Drug use-results survey of "Improvement of viraemia in chronic active hepatitis C"
*3: Post-marketing clinical study based on the instruction given at the approval of "Improvement of viraemia in chronic active hepatitis C"
*4: At the approval of "Improvement of viraemia in chronic hepatitis C (except in the patients with high blood HCV-RNA load)"
*5: At the approval of "Additional dosage and administration for childhood chronic hepatitis C"

Major abnormal clinical laboratory values*

(Source: interview form of OIF® (revised in December 2006))

	Chronic active hepatitis B		Chronic hepatitis C				
	At the approval	Drug use-results survey	At the approval of chronic active hepatitis*1	Drug use-results survey of chronic active hepatitis*2	Chronic active hepatitis post-marketing clinical study*3	At the approval of chronic persistent hepatitis*4	At the approval of childhood chronic hepatitis C*5
Leukopenia	42.7%	24.4%	27.6%	29.7%	59.3%	25.8%	5.4%
Thrombocytopenia	36.4%	22.4%	25.3%	35.7%	55.6%	22.7%	5.6%
Haemoglobin decreased	0.3%	0.4%	1.6%	4.0%	4.6%	5.2%	0.0%
Erythropenia	1.7%	0.9%	1.7%	3.4%	5.6%	2.1%	0.0%
Neutropenia	3.2%	4.0%	9.1%	2.1%	40.0%	7.6%	2.8%
AST (GOT) increased	5.8%	0.4%	0.6%	1.0%	0.0%	0.5%	0.0%
ALT (GPT) increased	5.8%	0.6%	0.6%	1.2%	0.9%	0.5%	0.0%
Proteinuria	2.2%	1.4%	4.8%	1.9%	7.4%	4.5%	0.0%
Cholesterol depletion			2.5%				

*1: At the approval of "Improvement of viraemia in chronic active hepatitis C"
*2: Drug use-results survey of "Improvement of viraemia in chronic active hepatitis C"
*3: Post-marketing clinical study based on the instruction given at the approval of "Improvement of viraemia in chronic active hepatitis C"
*4: At the approval of "Improvement of viraemia in chronic hepatitis C (except in the patients with high blood HCV-RNA load)"
*5: At the approval of "Additional dosage and administration for childhood chronic hepatitis C"

* The incidence of abnormal clinical laboratory values (except for Number of cases <100) was calculated from "Number of cases" as a denominator and "abnormal clinical laboratory values" as a numerator.

● Interferon Alfa-2b (genetical recombination) "Intron® A"

The incidence of adverse reactions in patients administered this product alone or concomitantly with rivavirin is as follows.

(Source: data obtained from Schering-Plough K.K.)

	Monotherapy with this product (before approval + after approval*1)	
	Chronic hepatitis C	Chronic active hepatitis B
Number of cases	5554	1084
Cases of adverse reaction etc.	4819	896
Incidence of adverse reaction etc.	86.8%	82.7%
Major adverse reaction		
Pyrexia	75.2%	72.7%
Malaise	14.5%	11.9%
Headache	7.7%	7.6%
Leukopenia	20.4%	40.4%
Granulocyte count decreased	4.3%	6.1%
Thrombocytopenia	22.6%	34.4%
Anaemia	5.4%	3.0%
AST (GOT) increased	0.6%	6.0%
ALT (GPT) increased	0.6%	6.3%
Appetite impaired	12.6%	10.9%
Alopecia	15.3%	7.0%
Arthralgia	5.0%	4.8%

*1: Based on the results from the investigation conducted until approval and the reinvestigation

*: Adverse reactions with incidence of ≥5% in a total of chronic hepatitis C or chronic active hepatitis B.

	Concomitant use with ribavirin (24 weeks: before approval*2)
	Chronic hepatitis C
Number of cases	271
Cases of adverse reaction etc.	271
Incidence of adverse reaction etc.	100.0%
Major adverse reaction	
Pyrexia	95.2%
General malaise	83.0%
Headache	73.1%
Chills	32.1%
Sleep loss	43.2%
Dizziness	25.8%
Nervousness	10.7%
Depression	10.0%
Hypoaesthesia	10.0%
Leukopenia	86.7%
Granulocyte count decreased	73.4%
Thrombocytopenia	67.9%
Anaemia**	67.2%
Iron metabolism disorder	55.0%
Reticulocyte count decreased	30.3%

Major adverse reaction	
Nausea/Vomiting	34.3%
Diarrhoea	22.9%
Stomatitis	19.2%
Constipation	18.5%
Pancreatic enzyme abnormality	14.4%
Alopecia	49.8%
Rash	29.9%
Itching	29.5%
Eczema	16.2%
Arthralgia	62.0%
Myalgia	32.8%
Back pain	26.9%
Cough	21.4%
Pharyngitis	20.3%
Dyspnoea	12.2%

Monocyte count increased	17.0%
Lymphocyte count increased	15.9%
Serum iron increased	15.5%
Lymphocyte count decreased	10.7%
Bilirubinaemia	22.5%
Appetite impaired	70.1%
Abdominal pain	43.9%

Thyroid function abnormal	21.0%
Hyperuricaemia	19.6%
Weight decreased	19.6%
Pain in skin, extremities, etc.	15.1%
Hot flush	13.7%
Taste disturbance	13.7%

*2: Overall results of the adverse reactions until approval (concomitant use: this product + ribavirin, administration for 24 weeks)
**: Including the abnormal clinical laboratory values for the subjective and objective symptoms of anaemia, plus erythropenia, haemoglobin decreased, haematocrit decreased, etc.

	Concomitant use with ribavirin (for 48 weeks: clinical study in Japan*3)
	Chronic hepatitis C
Number of cases	253
Cases of adverse reaction etc.	253
Incidence of adverse reaction etc.	100.0%
Major adverse reaction	
Pyrexia	99.2%
Malaise	97.6%
Chills	33.6%
Headache	94.1%
Sleep loss	74.3%
Dizziness	40.3%
Irritability	15.0%
Depression	11.5%
Lymphocyte count decreased	94.9%
Neutropenia	88.5%
Leukopenia	87.0%
Haemoglobin decreased	73.9%
Erythropenia	70.8%
Reticulocyte count increased	68.4%
Haematocrit decreased	67.2%
Thrombocytopenia	52.2%
Lymphocyte count increased	41.9%
Reticulocyte count decreased	33.6%
Basophil count increased	28.5%
Neutrophil count increased	28.1%
Eosinophil count increased	24.5%
Monocyte count increased	10.3%
Bilirubin increased	37.9%
LDH increased	15.8%
AST (GOT) increased	15.8%
ALT (GPT) increased	15.8%

Major adverse reaction	
Nausea/Vomiting	68.0%
Abdominal pain	59.7%
Diarrhoea	39.5%
Stomatitis/Cheilitis	30.4%
Constipation	24.9%
Thirst	22.5%
Stomach discomfort	21.3%
Dyspepsia	11.1%
Alopecia	73.9%
Rash	56.9%
Itching	51.0%
Dry skin	22.1%
Eczema	14.6%
Arthralgia	83.4%
Myalgia	78.3%
Back pain/low back pain	39.1%
Sensory aberrations	20.9%
Muscle spasticity	19.4%
Upper respiratory inflammation	47.8%
Cough	28.5%
Dyspnoea	22.1%
Epistaxis	13.8%
Sputum increased	12.6%
Eye pain	12.6%
Thyroid function abnormal	37.2%
Taste disturbance	29.2%

γ-GTP increase	13.4%
Flushing	18.2%
Tachycardia	15.8%
Chest pain	12.6%
Appetite impaired	90.5%

Weight decreased	26.5%
CRP increased	13.8%
Hyperuricaemia	12.6%
Fatigue	10.7%

*3: Overall results of the adverse reactions in clinical study in Japan (concomitant use: this product + ribavirin, administration for 48 weeks)

● Interferon alfacon-1 (genetical recombination) "Advaferon"

(Source: data obtained from the 8th Periodic Safety Update Report)

	Before approval	Special drug use-results survey*1
Number of cases	227	594
Cases of adverse reaction etc.	227	540
Incidence of adverse reaction etc.	100.0%	90.9%
Major adverse reaction		
Pyrexia	98.2%	81.3%
Malaise	45.4%	7.1%
Chills	9.3%	
Headache	39.2%	4.6%
Depressed mood	5.7%	4.4%
Insomnia	27.8%	6.6%
Anaemia	0.4%	2.7%
Alopecia	27.8%	1.5%
Dizziness	6.6%	1.2%
Red blood cell count decreased	0.9%	1.4%
Platelet count decreased	17.2%	62.6%
White blood cell count decreased	13.2%	57.2%
Neutrophil count decreased	11.9%	2.9%
Lymphocyte count increased	8.8%	
Aaemoglobin decreased	1.8%	1.4%
Haematocrit decreased	1.3%	1.5%
ALT increased	3.5%	2.4%
AST increased	5.3%	2.5%
Appetite impaired	39.7%	5.1%
Decreased appetite		4.0%

Major adverse reaction	Before approval	Special drug use-results survey*1
Stomach discomfort	20.3%	1.2%
Stomatitis	5.7%	0.7%
Diarrhoea	10.1%	2.2%
Nausea	14.1%	3.4%
Abdominal pain	8.4%	
Abdominal pain upper	1.8%	1.9%
Arthralgia	32.6%	2.2%
Back pain	15.0%	0.8%
Myalgia	14.1%	1.2%
Chest pain	3.1%	0.3%
Proteinuria	2.6%	1.0%
Hepatic function abnormal		2.0%
Pruritus	4.0%	1.9%
Injection site erythema	1.3%	1.2%
Cough	4.0%	
Weight decreased	15.9%	0.5%
Retinal haemorrhage	0.9%	1.2%
Gingival bleeding	4.0%	0.2%

*1: Cumulative data from the Special Drug Use-Results Survey conducted from October 2002 to September 2007

● Interferon Beta "Feron", "IFN β Mochida"

The incidence of major adverse reactions in the clinical studies in Japan conducted before the approval of Feron and the Post Marketing Surveillance, etc, are shown below.

(Source: data obtained from Toray Industries, Inc.)

	Chronic hepatitis C	Chronic active hepatitis B
Number of cases	2573	1392
Cases of adverse reaction etc.	2207	1278

Incidence of adverse reaction etc.	85.78%	91.81%
Major adverse reaction		
Pyrexia	72.87%	90.59%
Malaise	6.53%	1.72%
General malaise	19.08%	18.75%
Headache/Headache dull	26.43%	20.47%
Head discomfort	0.04%	--
platelet count decreased	26.12%	7.26%
Leukopenia	22.08%	9.84%
Neutropenia	9.25%	0.29%
Granulocyte count decreased	1.17%	0.86%
Serum albumin decreased	8.67%	0.14%
Hypoalbuminaemia	1.79%	0.07%
Arthralgia	15.12%	8.05%
Nausea/Vomiting	6.18%	4.53%
Queasy	0.39%	1.65%
Feeling queasy	0.08%	0.14%
Churning of stomach	0.16%	--
Appetite impaired	12.55%	14.08%
Appetite impaired	0.39%	--
Decreased appetite	0.12%	0.07%
AST (GOT) increased	5.29%	--
Serum AST (GOT) increased	0.43%	0.72%
AST (GOT) increased transient	0.04%	--
ALT (GPT) increased	5.17%	--
Serum ALT (GPT) increased	0.35%	0.72%
ALT (GPT) increased transient	0.04%	--
Proteinuria	24.87%	1.08%
Urinary protein increased	0.16%	--
Urinary protein positive	0.51%	--
Chills/Shivering	22.66%	15.45%
Chilliness	0.04%	0.22%

The periods of each follow-up are as follows.
Chronic hepatitis C: June 1986 to October 2001
Chronic active hepatitis B: June 1980 to December 1992

The incidence of adverse reactions in patients with chronic active hepatitis C received IFN β Mochida is shown below. (Source: data obtained from Mochida Pharmaceutical Co., Ltd.)

	Investigation until approval	Drug use-results survey
Number of cases	238	1040
Cases of adverse reaction etc.	238	906
Incidence of adverse reaction etc.	100.0%	87.1%
Major adverse reaction		
Pyrexia	99.6%	73.4%
General malaise	62.2%	5.1%
Chills	62.2%	1.4%
Headache/Headache dull	47.9%	5.2%

Major adverse reaction	Investigation until approval	Drug use-results survey
Appetite impaired	34.5%	3.5%
Nausea/Vomiting/Queasy	10.9%	0.5%
Diarrhoea	2.5%	0.1%
Arthralgia	3.8%	1.4%

Platelet count decreased	69.3%	15.5%	Myalgia	16.4%	1.5%
Leukopenia	61.3%	11.8%	Low back pain	1.7%	0.3%
Neutropenia	0.4%	1.2%	Pruritus	2.1%	0.2%
Gingival bleeding	1.3%	--	Skin eruption	2.5%	0.1%
Serum albumin decreased	7.6%	1.1%	Alopecia	2.5%	0.8%
Serum protein decreased	3.4%	0.3%	Injection site pain	1.7%	--
Elevated triglycerides	0.8%	1.2%	Weight decreased	8.0%	--
Anaemia	0.8%	1.3%	Neuralgia-like pain	5.0%	--
Proteinuria	21.4%	42.9%	Oedema	1.3%	0.1%

The periods of Drug Use-Results Survey: March 4, 1994 to March 26, 1996

● Peg-Interferon Alfa-2a (genetical recombination) “Pegasys”

(Source: data obtained from Chugai Pharmaceutical Co., Ltd.)

	Before approval	Drug use-results survey *1
Number of cases	279	1113
Cases of adverse reaction etc.	278	733
Incidence of adverse reaction etc.	99.6%	65.9%
Major adverse reaction		
Pyrexia	64.2%	8.5%
Malaise	61.7%	9.5%
Headache	61.3%	3.9%
Insomnia	27.2%	2.5%
Mood variable	7.2%	1.1%
Dizziness	6.1%	1.8%
Vertigo	9.0%	0.0%
White blood cell count decreased	72.8%	12.3%
Platelet count decreased	74.9%	23.4%
Lymphocyte count decreased	47.7%	0.3%
Neutrophil count decreased	78.9%	15.0%
Red blood cell count decreased	30.1%	2.3%
Abdominal pain	9.3%	0.5%
Abdominal pain upper	13.3%	0.5%
Stomach discomfort	10.0%	0.3%
Abdominal discomfort	5.7%	0.0%
Diarrhoea	26.2%	1.4%
Constipation	16.1%	0.7%
Toothache	5.4%	0.0%
Epistaxis	9.3%	0.6%
Eczema	8.6%	1.4%
Pruritus	21.2%	4.0%
Pruritus generalised	8.6%	0.3%
Rash	16.9%	3.2%
Pharyngolaryngeal discomfort	5.7%	0.0%
Nasopharyngeal pain	20.4%	0.5%

Major adverse reaction	Before approval	Drug use-results survey *1
Haematocrit decreased	30.8%	2.5%
Haemoglobin decreased	31.2%	3.8%
Arthralgia	31.2%	2.6%
Back pain	26.5%	0.9%
Myalgia	21.9%	1.0%
Pain in extremity	5.7%	0.4%
Musculoskeletal stiffness	8.6%	0.0%
Chills	7.5%	0.5%
Fatigue	6.5%	0.9%
Appetite impaired	14.0%	1.4%
Nausea	16.1%	1.0%
Vomiting	10.0%	0.0%
ALT increased	21.9%	2.1%
AST increased	23.7%	1.8%
Blood glucose increased	5.4%	0.5%
LDH increased	6.8%	0.8%
TSH increased	8.6%	0.5%
Blood elevated triglycerides	21.2%	0.3%
CRP increased	11.5%	0.0%
γ-GTP increase	17.6%	0.8%
Injection site erythema	19.0%	1.5%
Injection site pruritus	13.3%	0.7%
Hypoaesthesia	10.0%	0.5%
Retinal haemorrhage	5.0%	1.4%
Weight decreased	10.4%	0.4%
Palpitations	5.4%	0.5%

Pharyngitis	20.0%	0.5%
Cough	26.5%	0.4%
Productive cough	13.3%	0.3%
Upper respiratory tract infection	9.0%	0.0%

Blood phosphorus decreased	11.1%	0.0%
Protein urine present	6.1%	0.0%
Alopecia	37.3%	0.0%
Feeling hot	5.4%	0.4%

*1: Cumulative data from the Drug Use-Results Survey as of July 2007

● Peg-Interferon Alfa-2b (genetical recombination) "Pegintron"

The incidence of adverse reactions in the clinical studies in Japan conducted before the approval (all data were obtained from concomitant use with ribavirin).

(Source: data obtained from Schering-Plough K.K.)

	48-week administration	24-week administration
Number of cases	269	63
Cases of adverse reaction etc.	269	63
Incidence of adverse reaction etc.	100.0%	100.0%
Major adverse reaction		
Pyrexia	95.9%	93.7%
Malaise	93.7%	92.1%
Chills	32.0%	36.5%
Headache	90.0%	82.5%
Sleep loss	66.5%	63.5%
Dizziness	40.5%	41.3%
Depression	13.4%	7.9%
Irritability	12.6%	4.8%
Lymphocyte count decreased	96.7%	96.8%
Leukopenia	96.7%	92.1%
Neutropenia	88.8%	81.0%
Haemoglobin decreased	87.4%	77.8%
Erythropenia	81.0%	74.6%
Haematocrit decreased	79.9%	73.0%
Reticulocyte count increased	72.5%	63.5%
Platelet count decreased	46.1%	39.7%
Lymphocyte count increased	33.1%	33.3%
Basophil count increased	27.1%	27.0%
Reticulocyte count decreased	25.3%	20.6%
Eosinophil count increased	19.7%	20.6%
Neutrophil count increased	18.2%	22.2%
Monocyte count increased	11.9%	4.8%
Bilirubin increased	41.3%	44.4%
AST (GOT) increased	16.7%	11.1%
γ-GTP increase	17.1%	7.9%
LDH increased	16.0%	7.9%
ALT (GPT) increased	14.9%	6.3%
Tachycardia	21.2%	9.5%
Flushing	20.1%	11.1%
Chest pain	12.3%	4.8%
Appetite impaired	84.0%	73.0%

Major adverse reaction	48-week administration	24-week administration
Nausea/Vomiting	58.4%	39.7%
Abdominal pain	55.4%	36.5%
Diarrhoea	36.8%	12.7%
Stomatitis/Cheilitis	26.8%	22.2%
Constipation	22.7%	19.0%
Stomach discomfort	16.7%	17.5%
Thirst	15.6%	11.1%
Alopecia	68.0%	71.4%
Rash	56.9%	38.1%
Itching	60.2%	20.6%
Dry skin	19.7%	12.7%
Eczema	15.6%	7.9%
Erythema	10.8%	11.1%
Arthralgia	75.8%	74.6%
Myalgia	69.9%	61.9%
Back pain/low back pain	38.3%	28.6%
Sensory aberrations	17.1%	15.9%
Muscle spasticity	14.5%	9.5%
Upper respiratory inflammation	47.2%	33.3%
Cough	29.0%	17.5%
Dyspnoea	25.7%	22.2%
Epistaxis	11.2%	6.3%
Sputum increased	12.3%	0.0%
Injection site reaction (Erythema)	40.0%	25.4%
Injection site (Itching)	24.5%	25.4%
Thyroid function abnormal	38.3%	30.2%
Taste disturbance	26.8%	11.1%
Weight decreased	21.2%	11.1%
CRP increased	19.3%	15.9%
Fatigue	11.2%	9.5%
Infectious disease	10.8%	3.2%

2

Sudden onset of sleep, etc. associated with non-ergoline dopamine agonists (patients must be advised to refrain from driving, etc.)

	Ingredient name	Brand name (name of company)
Active Ingredient **Brand Name (name of company)**	① Pramipexole Hydrochloride Hydrate ② Ropinirole Hydrochloride ③ Talipexole Hydrochloride	① BI·Sifrol Tablets 0.125 mg and 0.5 mg (Nippon Boehringer Ingelheim Co., Ltd.) ② ReQuip Tablets 0.25 mg, 1 mg, and 2 mg (GlaxoSmithKline K.K.) ③ Domin Tablets 0.4 (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Central nervous system agents-Antiparkinsonian agents	
Indications	Parkinson's disease	

1. History

① Pramipexole Hydrochloride Hydrate, ② Ropinirole Hydrochloride and ③ Talipexole Hydrochloride are non-ergoline dopamine agonists used as a treatment for Parkinson's disease. These drugs have been marketed with the indication for Parkinson's disease since ① January 2004, ② December 2006 and ③ June 1996, respectively.

The MHLW has alerted healthcare providers about ③ Talipexole Hydrochloride by calling for the marketing authorisation holder to include language stating that "Sleepiness may occur. Patients should be advised to refrain from potentially hazardous activities including driving." in the General Precautions section under the PRECAUTIONS of the package insert of this product since the date of initial marketing. In February 2002, the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency (EMEA) published CPMP POSITION STATEMENT DOPAMINERGIC SUBSTANCES AND SUDDEN SLEEP ONSET (http://www.emea.europa.eu/pdfs/human/press/pos/057802.pdf). In view of the statement, the MHLW has called for an alert in March 2003 by directing inclusion of additional description on "episodes of sudden onset of sleep" in the Clinically Significant Adverse Reactions section, and language stating that "Episodes of sudden onset of sleep may occur. Patients should be advised to refrain from potentially hazardous activities including driving." in the Important Precautions section under PRECAUTIONS of the package insert of this product. The MHLW has also alerted healthcare providers about ① Pramipexole Hydrochloride Hydrate and ② Ropinirole Hydrochloride since the initial marketing by calling for including language stating that "Patients should be advised to refrain from potentially hazardous activities including driving while taking this drug." in the Warning section, and language stating that "Patients should be adequately informed of possible episodes of sudden onset of sleep and somnolence while taking this drug, and should be advised to refrain from potentially hazardous activities including driving." in the Important Precautions section, together with the description on episodes of sudden onset of sleep, etc. in Clinically Significant Adverse Reactions section under PRECAUTIONS. In spite of these actions, there have been some reports that patients on medications with these drugs developed episodes of sudden onset of sleep and caused automobile accidents while driving. Therefore, on February 12, 2008, the MHLW has called for a further alert by directing relevant companies to implement a revision of PRECAUTIONS of these products to ensure that patients must refrain from potentially hazardous activities including driving, operating machines and working at heights while taking these products. Specific safety measures are shown below.

2. Adverse reaction reports

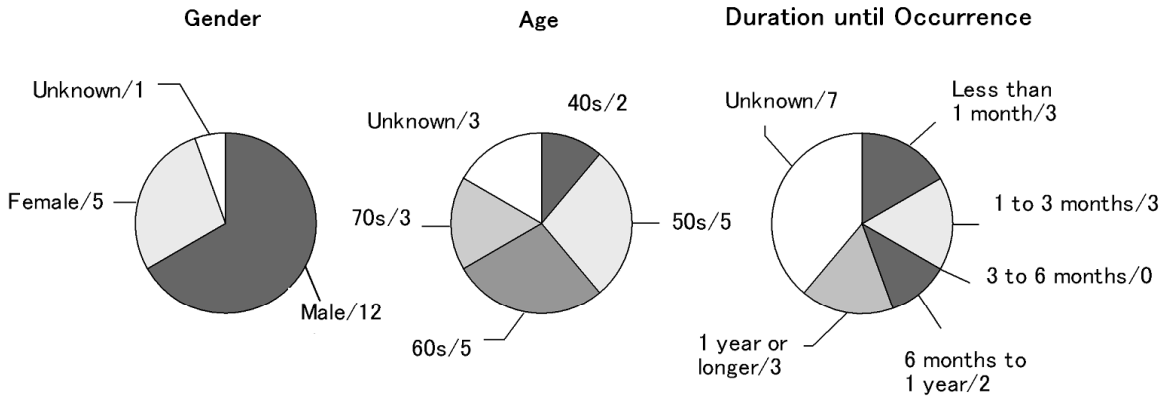
Adverse reaction reports related to automobile accidents in 2004 and thereafter are tabulated in Table 1. A total of 18 cases have been reported in patients taking ① Pramipexole Hydrochloride Hydrate, and one in a patient taking ② Ropinirole Hydrochloride and one in a patient taking ③ Talipexole Hydrochloride. It should be noted that the one case of ③ Talipexole Hydrochloride occurred in the patient who was on a concomitant therapy with ① Pramipexole Hydrochloride Hydrate.
Gender, age and the duration until the occurrence of the 18 patients who developed adverse reactions resulting in automobile accidents while taking ① Pramipexole Hydrochloride Hydrate are shown in Figure 1.
For reference, Table 2 indicates part of reported cases of the adverse reactions.

Table 1 Profile of adverse reactions resulting in automobile accidents in patients treated with non-ergoline dopamine agonists that occurred in 2004 and thereafter

Year of Occurrence / Product Name	2004	2005	2006	2007	Unknown	Total
Pramipexole Hydrochloride Hydrate	2 (9000)	5 28000	3 43000	6 73000	2	18
Ropinirole Hydrochloride	—	—	0 (unknown)	1 (9000)	0	1
Talipexole Hydrochloride	0 (13000)	0 (10000)	0 (9000)	1 (8000)	0	1(Note)

Upper column: The number of reported adverse reaction resulting in automobile accidents
Lower column ( ): The annual number of users of the drug estimated by the relevant companies
(Note): The total number since the marketing in 1996 is 4.

Figure 1 Adverse reactions resulting in automobile accidents in patients treated with Pramipexole Hydrochloride Hydrate



3. Safety measures

Patients treated with non-ergoline dopamine agonists must be advised:
(1) that sudden onset of sleep without warning signs and somnolence, etc. may occur.
(2) that there have been some reports of automobile accidents due to sudden onset of sleep, etc. in patients on treatment with this drug, and that patients must refrain from potentially hazardous activities including driving.

On February 12, 2008, the MHLW has called for relevant companies of these products to revise the Warning or the Important Precautions sections to include language stating that automobile accidents in patients who experienced sudden onset of sleep, etc. have been reported, and patients should be adequately advised of sudden onset of sleep, etc. The MHLW has also called for immediate issue of Dear Healthcare Professional Letters for ① Pramipexole Hydrochloride Hydrate to ensure that healthcare

providers are aware of the information.
No particular tendencies for age/gender of patients, the duration until the occurrence and the doses at the time of the accident have been observed in automobile accidents in patients who experienced sudden onset of sleep, etc. Healthcare providers should be encouraged to adequately advise patients on treatment with this drug to refrain from engaging in potentially hazardous activities including driving.

<< **PRECAUTIONS** (underlined parts are additions) >>

① **Pramipexole Hydrochloride Hydrate**

[Warning]

WARNING

Sudden onset of sleep without warning signs and somnolence, etc. may occur. There have been reports of automobile accidents in patients who experienced sudden onset of sleep, etc. Patients must be adequately informed of the possible occurrence of sudden onset of sleep and somnolence, etc. associated with this product, and advised to refrain from engaging in potentially hazardous activities such as driving a car, operating machines and working at heights while taking this drug.

[Important Precautions]

There have been reports of automobile accidents in patients who experienced sudden onset of sleep, etc. Cases of occurrence of sudden onset of sleep include those without warning signs such as somnolence and excessive sleepiness, and those occurring one year or longer after administration of this product. Patients must be adequately informed of the possible occurrence of sudden onset of sleep and somnolence, etc. associated with this product, and advised to refrain from engaging in potentially hazardous activities such as driving a car, operating machines and working at heights.

② **Ropinirole Hydrochloride**

[Warning]

WARNING

Sudden onset of sleep without warning signs and somnolence, etc. may occur. There have been reports of automobile accidents in patients who experienced sudden onset of sleep. Patients must be adequately informed of the possible occurrence of sudden onset of sleep and somnolence, etc. associated with this product, and advised to refrain from engaging in potentially hazardous activities such as driving a car, operating machines and working at heights while taking this drug.

[Important Precautions]

There have been reports of automobile accidents in patients who experienced sudden onset of sleep. Patients must be adequately informed of the possible occurrence of sudden onset of sleep and somnolence, etc., and advised to refrain from engaging in potentially hazardous activities such as driving a car, operating machines and working heights. Cases of occurrence of sudden onset of sleep reported in foreign countries include those without warning signs such as somnolence and excessive sleepiness, and those occurring one year or longer after administration of this product.

③ **Talipexole Hydrochloride**

[Important Precautions]

Sudden onset of sleep without warning signs, somnolence, decreased attention/concentration/reflex function, light-headed feeling, dizziness and orthostatic hypotension may occur. There have been reports of automobile accidents in patients who experienced sudden onset of sleep, etc. Cases of occurrence of sudden onset of sleep include those without warning signs such as somnolence and excessive sleepiness. Patients must be adequately informed of the possible occurrence of sudden onset of sleep and somnolence, etc. associated with this product, and advised to refrain from engaging in potentially hazardous activities such as driving a car, operating machines and working at heights.

Table 2 Case Summary

① Pramipexole Hydrochloride Hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Parkinson's disease (constipation)	1.5 mg 427 days ↓ 2 mg 28 days ↓ 2.5 mg 510 days ↓ 3 mg 57 days ↓ 3.5 mg 195 days ↓ 4 mg 28 days ↓ 1.5 mg 27 days	**Sudden onset of sleep** **(automobile accident, laceration of the lower jaw)** On day 1 of administration: The drug was initiated at 1.5 mg/day (switched from bromocriptine 7.5 mg/day). On day 427 of administration: The dose was increased to 2 mg/day. On day 455 of administration: The dose was increased to 2.5 mg/day. On day 965 of administration: The dose was increased to 3 mg/day. On day 1022 of administration: The dose was increased to 3.5 mg/day. On day 1217 of administration: The dose was increased to 4 mg/day. On day 1243 of administration: The patient drove home for about 1 hour and 30 minutes. Two or three minutes before arriving home, sleep occurred without preceding sleepiness when she was going into a gentle right-hand curve on a street. When she woke up, she was crashing into a guardrail and the car was completely destroyed. She had a laceration of the lower jaw. The accident occurred when she was driving at about 50 km/h. She had not drunk alcohol within a few hours before the accident. She was not receiving concomitant insulin treatment. Sleep status of the patient before the accident: ▪ Quality: Nocturnal awakening due to painful dystonia ▪ Napping: None Before onset of the accident: ▪ Sleepiness or unintended sleep occurred when she was operating a computer or using a cell-phone. On day 1245 of administration: The dose was decreased to 1.5 mg/day. Pergolide 750 μg/day was initiated. On day 1272 of administration (day of discontinuation): The drug was discontinued and pergolide was increased to 1500 μg/day. Sudden onset of sleep did not develop afterwards. The patient was recovering from laceration of the lower jaw.
	Concomitant medications: levodopa/carbidopa, amantadine hydrochloride, diazepam, selegiline hydrochloride, entacapone			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Parkinson's disease (hypertension, hyperlipidaemia, constipation, reflux oesophagitis, gastric ulcer)	0.125 mg 7 days ↓ 0.5 mg 7 days ↓ 1 mg 7 days ↓ 1.5 mg 7 days ↓ 2 mg 17 days ↓ 2.5 mg 7 days ↓ 3 mg 210 days ↓ 1.5 mg 56 days ↓ 2 mg 55 days	**Sudden onset of sleep (automobile accident)** On day 1 of administration: The patient did not report sleepiness. About one year after administration: The patient drove after a long interval home from the hospital. He experienced sudden onset of sleep on the way and scratched the car on a guardrail. The sound of scratching on the guardrail of the opposite (right) lane woke him up. Sleep status of the patient before the accident (within one week of the previous day of the accident) ▪ Average hours of sleep per night: 10 hours ▪ Quality of sleep: Good, even when he got up to urinate once or twice ▪ Napping: He often napped after lunch for 30 to 60 minutes.
	Concomitant medications: bisoprolol fumarate, nifedipine, valsartan, atorvastatin calcium hydrate, ethyl icosapentate, heavy magnesium oxide, sodium rabeprazole			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 60s	Parkinson's disease (constipation)	0.25 mg Continuous administration	**Somnolence (automobile accident)** The patient never reported sleepiness before initiation of the drug. On day 1 of administration: The drug was initiated at 0.25 mg/day. On day about 60 of administration: The patient had an automobile accident due to somnolence about 15 minutes after leaving home by car. He crashed into a power pole at about 40 km/h.
	Concomitant medications: cabergoline, trihexyphenidyl hydrochloride, magnesium oxide, levodopa/carbidopa			

② **Ropinirole Hydrochloride**

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 50s	Parkinson's disease (hypercholesterolaemia)	1.5 mg 43 days	**Sudden onset of sleep (automobile accident)** On day 1 of administration: The drug was initiated at 1.5 mg for treatment of Parkinson's disease. On day 37 of administration: When the patient was driving, he suddenly lost consciousness 30 minutes after taking the drug. He regained consciousness when he rear-ended a stopped car. There was no physical harm to the patient. On day 43 of administration (day of discontinuation): The drug was discontinued.
	Concomitant medications: levodopa/carbidopa, selegiline hydrochloride, trihexyphenidyl hydrochloride, atorvastatin calcium hydrate			

③ **Talipexole Hydrochloride**

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
5	Male 40s	Parkinson's disease (none)	0.8 mg 50 days ↓ 0.4 mg 7 days	**Sudden onset of sleep (automobile accident)** On day 1 of administration: Talipexole hydrochloride was initiated at 0.8 mg for treatment of Parkinson's disease. The patient had been taking pramipexole hydrochloride hydrate at 3 mg for 203 days prior to initiation of talipexole hydrochloride. On unknown days: The patient crashed into a power pole near his home and the garage of his home when he was driving his car. Both accidents caused only small dents and scratches on the car and no traumatic injury to the patient occurred because he was driving at low speed. He reported that, as he thought back, he had lost consciousness for a moment and regained consciousness after the crash. He did not report the accidents to his physician during his visit. On day 48 of administration: The patient had not slept enough for about 2 weeks and had only about 4 hours of sleep the night before. He was treated with the drug at 0.8 mg but he reported that he had sometimes missed doses and had not taken the drug the day before. He took levodopa/carbidopa 100 mg after awakening, levodopa/carbidopa 50 mg, entacapone 200 mg, pergolide 250 μg, and pramipexole hydrochloride hydrate 0.5 mg after breakfast and drove to work. When he was driving the speed limit (about 40 km/h), he rear-ended a car. He said that, as far as he remembered, he had fallen asleep for a moment after seeing the car in front slowing down at a traffic light, woken up, and braked but could not avoid the accident. He did not suffer any traumatic injury. The driver of the rear-ended car reportedly had a minor whiplash injury.

				On day 50 of administration: The patient visited the hospital in the morning. He reported the accident that occurred on day 48 of administration to his physician. The physician decreased the dose of pramipexole hydrochloride hydrate from 3 mg/day to 1.5 mg/day and talipexole hydrochloride from 0.8 mg/day to 0.4 mg/day. On day 57 of administration (day of discontinuation): Pramipexole hydrochloride hydrate and talipexole hydrochloride was discontinued. So far, no sudden onset of sleep or sleepiness occurred after discontinuation.
	Concomitant medications: pramipexole hydrochloride hydrate, entacapone, zonisamide, clonazepam, pergolide, amantadine hydrochloride, levodopa/carbidopa			

3

Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated February 12, 2008.

1 Cyclophosphamide (oral dosage form), Cyclophosphamide (injectable dosage form)

❶ Cyclophosphamide (oral dosage form)

Brand Name (name of company)	Endoxan tablets 50 mg (Shionogi & Co., Ltd)
Therapeutic Category	Alkylating agents
Indications	Remission of subjective and objective symptoms of the following diseases: multiple myeloma, malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulosarcoma), breast cancer, acute leukaemia, polycythaemia vera, lung cancer, neural tumour (neuroblastoma, retinoblastoma), bone tumour It should be noted that this product must be used concurrently with other anti-tumour agents for the following diseases: chronic lymphocytic leukaemia, chronic myeloid leukaemia, pharyngeal cancer, gastric cancer, pancreatic carcinoma, liver carcinoma, colon cancer, uterine cervical cancer, endometrial cancer, ovarian cancer, testicular tumour, trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, hydatidiform mole), rhabdomyosarcoma, malignant melanoma

<< **PRECAUTIONS** (underlined parts are additions) >>

[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder and jaundice may occur. Patients should be carefully monitored by hepatic function tests, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed. **Renal failure acute:** Serious renal disorder such as renal failure acute may occur. Patients should be carefully monitored by renal function tests, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.

❷ Cyclophosphamide (injectable dosage form)

Brand Name (name of company)	Endoxan injection 100 mg and 500 mg (Shionogi & Co., Ltd)
Therapeutic Category	Alkylating agents
Indications	1. Remission of subjective and objective symptoms of the following diseases: multiple myeloma, malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulosarcoma), lung cancer, breast cancer, acute leukaemia, polycythaemia vera, uterine cervical cancer, endometrial cancer, ovarian cancer, neural tumour (neuroblastoma, retinoblastoma), bone tumour

	It should be noted that this product must be used concurrently with other anti-tumour agents for the following diseases: chronic lymphocytic leukaemia, chronic myeloid leukaemia, pharyngeal cancer, gastric cancer, pancreatic carcinoma, liver carcinoma, colon cancer, testicular tumour, trophoblastic diseases (choriocarcinoma, destructive hydatidiform mole, hydatidiform mole), rhabdomyosarcoma, malignant melanoma 2. Concomitant therapy with other anti-tumour agents for the following malignant tumours: breast cancer (preoperative or postoperative chemotherapy for operable patients) 3. Conditioning regimen prior to hematopoietic cell transplantation for the following diseases: acute leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, severe aplastic anaemia, malignant lymphoma, hereditary diseases (immunodeficiency, inborn errors of metabolism, and congenital blood diseases: Fanconi's anaemia, Wiskott-Aldrich syndrome, mucopolysaccharidosis II , etc.)

<< **PRECAUTIONS** (underlined parts are additions) >>

[Adverse Reactions (clinically significant adverse reactions)]

Hepatic function disorder, jaundice: Hepatic function disorder and jaundice may occur. Patients should be carefully monitored by hepatic function tests, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.
Renal failure acute: Serious renal disorder such as renal failure acute may occur. Patients should be carefully monitored by renal function tests, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed.
Myocardial disorder, cardiac failure, cardiac tamponade, pericarditis: Myocardial disorder, cardiac failure, cardiac tamponade, pericarditis and pericardial effusion may occur. Patients should be carefully monitored, and appropriate measures, such as discontinuing treatment, should be taken if any abnormal findings are observed. Extra caution should be exercised when treating patients with a high dose of this product (conditioning regimen prior to hematopoietic cell transplantation).

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2004 to December 1, 2007) (events for which a causality to the drug could not be denied)
- Renal failure acute: 3 cases (no fatal case) [Injectable dosage form: 2 cases, unknown: 1 case]
- Cardiac tamponade, pericarditis, pericardial effusion: 2 cases (no fatal case)

The number of patients treated with cyclophosphamide for a year estimated by MAH: approximately 12000 for ❶
approximately 66000 for ❷
(February 2007 to January 2008)
Marketed in Japan in: October 1992 for ❶
1962 for ❷

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 50s	Peripheral blood stem cell apheresis (chronic renal failure, prostatic hypertrophy, hypertension)	3000 mg 2 days	**Renal failure acute** Medical history: diabetes mellitus Unknown time: Chronic renal failure developed. About 5 months before administration: Multiple myeloma developed. On day 1 of administration: The patient started cyclophosphamide (injectable dosage form) 3000 mg/day for peripheral blood stem cell apheresis, mesna 1300 mg TID for prevention of adverse effects of cyclophosphamide, and granisetron hydrochloride 3 mg/day for prevention of queasy (each agent for two days). He experienced pyrexia of 38ºC with chills at night and took acetaminophen 400 mg for one day. On day 2 of administration (day of completion of administration): After completion of cyclophosphamide injection, stools watery and vomiting occurred with increasing frequency (a total of 11 bowel movements). Abdominal pain developed. 1 day after completion: Vomiting and diarrhoea persisted. Frequency of bowel movements was 10 times a day. Body temperature was decreasing with the highest temperature of 37.2ºC. However, acute aggravation of chronic renal failure occurred with laboratory evidence of rapid increases in blood BUN and creatinine. The patient started receiving pazufloxacin mesilate 600 mg/day for 9 days and trandolapril 0.5 mg/day. 2 days after completion: Diarrhoea gradually subsided but queasy persisted. The patient received central venous nutrition for 3 days because he could not eat. He was recovering from fever. 4 days after completion: BUN and creatinine level increased. Urine output was 350 mL/day. 6 days after completion: Dialysis was initiated at 3 times per week. 12 days after completion: The patient resumed eating. 38ºC of fever persisted for 7 days due to unknown cause and gradually subsided with infusion of antibiotics. 30 days after completion: Dialysis was discontinued because daily urine output was gradually increasing and the creatinine level was stable. 37 days after completion: The patient recovered from acute aggravation of chronic renal failure but with sequelae.
	Concomitant medications: mesna, granisetron hydrochloride, amlodipine besilate, lansoprazole, acetaminophen			

Clinical Laboratory Values

	6 days before administration	1 day after completion	5 days after completion	12 days after completion	28 days after completion	37 days after completion
BUN (mg/dL)	16	32	51	52	34	38
Serum creatinine (mg/dL)	1.6	3.6	7.7	10.5	4.5	4.9

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 50s	Bone marrow conditioning regimen (none)	2200 mg 2 days	**Cardiac tamponade, pericardial effusion** Medical history: liver disorder (cefozopran hydrochloride) About 9 months before administration: The patient experienced general malaise and visited a local hospital. Abnormalities were noted on a blood test. She was referred to our hospital and had a diagnosis of acute myeloid leukaemia. Chemotherapy was initiated. About 5 months before administration: A bone marrow test revealed remission. Chemotherapy was continued. 10 days before administration: The patient was hospitalized for allogenic bone marrow transplantation from an unrelated donor. 5 days before administration: The patient underwent total body radiation therapy (2 Gy twice daily for 3 days). 3 days before administration: The patient started receiving acyclovir 200 mg 5 times daily for prevention of herpes virus infection (16 days). On day 1 of administration: The patient started receiving cyclophosphamide (injectable dosage form) 2200 mg/day for bone marrow conditioning and mesna 1260 mg TID for prevention of cystitis haemorrhagic due to this drug (both agents for 2 days). 1 day after completion: The patient started receiving tacrolimus hydrate 1.1 mg for prevention of graft versus host disease (the dose was adjusted as needed based on blood level thereafter). 3 days after completion: The patient underwent allogeneic bone marrow transplantation from a donor from the bone marrow bank. 4 days after completion: The patient started receiving methotrexate 12 to 18 mg/day for prevention of graft versus host disease (a total of 3 times at intervals of 1 to 2 days). 10 days after completion: The patient complained of epigastric and right upper quadrant pain. CT and echocardiography showed pericardial effusion and duodenal hypertrophy. She was then treated with antibiotics and other agents but hypotension persisted. Dopamine hydrochloride was initiated at a low dose. 29 days after completion: Blood pressure decreased and urine output decreased. Repeated echocardiography revealed increased pericardial effusion. Doses of dopamine hydrochloride and diuretics were increased.

				30 days after completion: The patient underwent pericardiocentesis to remove 300 mL of fluid. After the procedure, blood pressure and urine output was recovering. However, dopamine hydrochloride was continued. 39 days after completion: Cardiac tamponade (blood pressure decreased, urine output decreased, and cardiac failure) had not resolved.
	Concomitant medications: mesna, acyclovir			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 30s	Bone marrow conditioning regimen (none)	2900 mg 2 days	**Pericarditis** Medical history: None About 2 years before administration: The patient experienced general malaise and visited a local hospital. White blood cell increased was noted and she was referred to our hospital. Chronic myeloid leukaemia was diagnosed. She was hospitalized for bone marrow transplant and underwent total body radiation therapy (12 Gy). On day 1 of administration: This drug (injectable dosage form) was administered for bone marrow conditioning at 2900 mg/day for 2 days. 4 days after completion: The patient underwent bone marrow transplant from her HLA-matched mother (147×10^8 nucleated cells were infused). 6 days after completion: The patient developed pyrexia. Antibiotics and G-CSF were initiated. 9 days after completion: Pain precordial developed. Pericarditis was diagnosed based on ST elevation on a 12-lead ECG. Diclofenac sodium and prednisolone 30 mg/day were initiated (4 days). 12 days after completion: Chest pain disappeared. About 4 months after completion: The patient recovered from acute pericarditis. She was discharged from the hospital.
	Concomitant medications: None			

4

Revision of PRECAUTIONS (No. 195)

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 Notification dated February 12, 2008 (excluding those presented in "2. Sudden onset of sleep, etc. associated with non-ergoline dopamine agonists (patients must be advised to refrain from driving, etc.)" and in "3. Important Safety Information".

1 <Vasodilators> Nicorandil (oral dosage form)

[Brand Name]	SIGMART Tablets 2.5 mg and 5 mg (Chugai Pharmaceutical Co., Ltd.) and others
[Adverse Reactions (clinically significant adverse reactions)]	**Oral ulcer, tongue ulceration, anal ulcer, gastrointestinal ulceration:** Oral ulcer, tongue ulceration, anal ulcer, gastrointestinal ulceration may occur. If these symptoms occur, administration of this drug should be discontinued and appropriate measures should be taken.

2 <Synthetic antibacterials> Moxifloxacin Hydrochloride (oral dosage form)

[Brand Name]	AVELOX Tablets 400 mg (Bayer Yakuhin, Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Hypoglycaemia:** Serious hypoglycaemia may occur (particularly in the elderly and patients with diabetes mellitus). Patients should be carefully monitored, and administration of this drug should be discontinued, and appropriate measures should be taken if any abnormal findings are observed.

5

List of products subject to Early Post-marketing Phase Vigilance

(As of March 1, 2008)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Tadalafil Cialis Tablets 5 mg, 10 mg, and 20 mg	Eli Lilly Japan K.K.	September 12, 2007
Topiramate Topina Tablets 50 mg and 100 mg	Kyowa Hakko Kogyo Co., Ltd.	September 26, 2007
Montelukast Sodium Kipres Fine Granules 4 mg	Kyorin Pharmaceutical Co., Ltd.	October 2, 2007
Montelukast Sodium Singulair Fine Granules 4 mg	Banyu Pharmaceutical Co., Ltd.	October 2, 2007
Rocuronium Bromide Eslax Intravenous 25 mg/2.5 mL and 50 mg/5.0 mL	Nippon Organon K.K.	October 2, 2007
Garenoxacin Mesilate Hydrate Geninax Tablets 200 mg	Toyama Chemical Co., Ltd.	October 5, 2007
Idursulfase (Genetical recombination) Elaprase Solution for Intravenous Drip 6 mg	Genzyme Japan K.K.	October 17, 2007
Pilocarpine Hydrochloride Salagen Tablets 5 mg[*1]	Kissei Pharmaceutical Co., Ltd.	October 19, 2007
Nicorandil Sigmart Injection 2 mg, 12 mg, and 48 mg[*2]	Chugai Pharmaceutical Co., Ltd.	October 19, 2007
Clopidogrel Sulfate Plavix Tablets 25 mg and 75 mg[*3]	Sanofi-Aventis K.K.	October 19, 2007
Loratadine Claritin Tablets 10 mg, Claritin RediTab Tablets 10 mg[*4]	Schering-Plough K.K.	October 19, 2007
Travoprost Travatanz Ophthalmic Solution 0.004%	Alcon Japan Ltd.	October 25, 2007
Strontium (^{89}Sr) Chloride Metastron Injectable	Nihon Medi-Physics Co., Ltd.	October 31, 2007
Eplerenone Selara Tablets 25 mg, 50 mg, and 100 mg	Pfizer Japan Inc.	November 13, 2007
Estradiol Divigel 1 mg	Pola Pharma Inc.	November 20, 2007
Imiquimod Beselna Cream 5%	Mochida Pharmaceutical Co., Ltd.	December 10, 2007
Darunavir Ethanolate Prezista Tablets 300 mg	Janssen Pharmaceutical K.K.	December 10, 2007
Insulin Detemir (Genetical recombination) Levemir 300, Levemir 300 FlexPen	Novo Nordisk Pharma Ltd.	December 14, 2007

Nelarabine Arranon G Injection 250 mg	GlaxoSmithKline K.K.	December 14, 2007
Erlotinib Hydrochloride Tarceva Tablets 25 mg, 100 mg, and 150 mg	Chugai Pharmaceutical Co., Ltd.	December 18, 2007
Methylphenidate Hydrochloride Concerta Tablets 18 mg and 27 mg	Janssen Pharmaceutical K.K.	December 19, 2007
Beraprost Sodium Careload LA Tablets 60 μg	Toray Industries, Inc.	December 19, 2007
Beraprost Sodium Berasus LA Tablets 60 μg	Kaken Pharmaceutical Co., Ltd.	December 19, 2007
Dienogest Dinagest Tab. 1mg	Mochida Pharmaceutical Co., Ltd.	January 21, 2008
Loratadine Claritin Dry Syrup 1%	Schering-Plough K.K.	January 21, 2008
Gadoxetate Sodium EOB·Primovist Inj. Syringe	Bayer Yakuhin, Ltd.	January 25, 2008
Cinacalcet Hydrochloride Regpara Tablets 25 mg and 75 mg	Kirin Pharma Company, Limited	January 25, 2008
Montelukast Sodium Kipres Tablets 10[*5]	Kyorin Pharmaceutical Co., Ltd.	January 25, 2008
Montelukast Sodium Singulair Tablets-10[*5]	Banyu Pharmaceutical Co., Ltd.	January 25, 2008
Sorafenib Tosilate Nexavar 200 mg	Bayer Yakuhin, Ltd.	February 25, 2008

*1: An additional indication for “the treatment of symptoms of dry mouth in patients with Sjogren’s syndrome”
*2: An additional indication for “cardiac failure acute (including acute exacerbation of cardiac failure chronic)”
*3: An additional indication for “acute coronary syndrome (unstable angina pectoris, non ST segment elevation myocardial infarction) to which percutaneous coronary intervention (PCI) is being planned”
*4: Additional administration for “pediatrics”
*5: An additional indication for “rhinitis allergic”