Pharmaceuticals and Medical Devices Safety Information

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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).

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.

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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 December 1, 2006.

1 Tocilizumab (Genetical recombination)

Brand Name (name of company)	Actemra for Intravenous Infusion 200 (Chugai Pharmaceutical Co., Ltd.)
Therapeutic Category	Biological preparations-Miscellaneous
Indications	Improvement of symptoms and laboratory findings of Castleman's disease (increased CRP and fibrinogen, RBC sedimentation, decreased hemoglobin and albumin, and general malaise). This drug is only indicated for patients who are not suitable for lymphadenectomy.

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

[Warning]

WARNING

Infectious disease

Serious infectious diseases such as sepsis and pneumonia have been reported in patients treated with tocilizumab. Tocilizumab exerts its therapeutic effect by inhibiting the effects of IL-6. IL- 6 is a cytokine, which induces acute phase reactions (e.g., pyrexia, CRP increased).Tocilizumab inhibits these reactions, resulting in a suppression of symptoms associated with infectious diseases. This may delay detection of the infectious diseases and cause serious conditions. Therefore, patients should be carefully observed and interview of patients should be made during treatment with this drug. Even when only minor symptoms and no acute phase reactions are noted, changes in WBC and neutrophil counts should be monitored. If an infectious disease is suspected, patients should be examined by chest X-ray and CT scan etc. and appropriate measures should be taken.

[Contraindications]

Patients with a complicated serious infectious disease

[Careful Administration]

Patients with a complicated infectious disease or suspected infectious disease

[Important Precautions]

Since administration of this drug to patients with a complicated infectious disease may aggravate the infectious disease and lead to serious conditions, the following precautions should be observed.

(1) The presence or absence of infectious diseases such as pneumonia should be confirmed before starting this drug. Since clinical symptoms of Castleman's disease (e.g., pyrexia, malaise, and swollen lymph nodes) are similar to infectious symptoms, differential diagnosis should be carefully performed.

(2) If patients have a complicated infectious disease, treatment of such disease should be a priority.

<Reference Information>

The number of reported adverse reaction cases between June 2005 (initial marketing in Japan) and October 2006 (events for which a causality to the drug could not be denied)

- Serious infectious disease: 6 cases (of which 1 had a fatal case)

The number of patients treated with Tocilizumab for a year estimated by MAH (Marketing Authorisation Holder): 137 (November 2005 to October 2006)

Marketed in Japan in: June 2005

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 50s	Castleman's disease (diabetes mellitus, osteoporosis, headache)	390 mg 27 days (twice) 400 mg 73 days (6 times)	**Pneumonia** Approx. 10 years before administration: The patient was diagnosed with Castleman's disease (plasma cell type). There were no associated symptoms. Approx. 9 months before administration: The patient developed pneumonia aspergilla (left lung). IVH was inserted due to difficult peripheral IV access on hospitalization. The patient received a treatment with micafungin sodium and voriconazole. Methylprednisolone sodium succinate was administered for the treatment of Castleman's disease. Approx. 7 months before administration: The patient was hospitalized with suspected recurrent pneumonia aspergilla (left lung) due to cough, sputum, and increased opacity on left chest by chest X-ray (left lung). Sputum culture: aspergillus (−), tuberculin test: (−), Gaffky: (−), respiratory discomfort, sputum bloody, and decreased blood gases . Approx. 6 months before administration: Chest CT was performed. No apparent improvement of pneumonia aspergilla was observed. The patient received an 18-stitch suture for her cut from fall. Haemoglobin was 8.4 g/dL after blood transfusion. Treatment was given by infusion of prednisolone sodium succinate at 25 mg. Approx. 4 months before administration: IVH was removed. Infusion of prednisolone sodium succinate at 30 mg was given. Approx. 3 months before administration: Since no improvement of pneumonia aspergilla was observed, a left upper lobe segment was removed by thoracotomy at another hospital. The patient developed anaemia (haemoglobin 5.6 g/dL), which did not improve even after blood transfusion. Blood transfusion was performed before and after the surgery. She had no post-operative wound problems and was retransferred to our hospital. Oral administration of sulfamethoxazole/trimethoprim was started (until 94 days after administration). Approx. 2 months before administration: The patient received treatment and rehabilitation for Castleman's disease. She was moved to a single room because of white blood cell decreased and platelets decreased and pneumonia.	Company report

				Antibiotics and antifungal agent were administered. Steroid pulse therapy was performed for pancytopenia. The symptoms gradually recovered. Unknown: Cyclophosphamide was discontinued due to white blood cell decreased (date of initiation is unknown). 45 days before administration: Treatment was given by infusion of prednisolone sodium succinate at 60 mg. Approximately 1 month before administration: KL-6 300 U/mL, β-D-glucan 8.7 pg/mL. 12 days before administration: Treatment was given by infusion of prednisolone sodium succinate at 50 mg (until 3 days after administration). 1 day before administration: General malaise [Performance Status (PS): 3], anorexia, headache only at dawn were manifested. On day 1 of administration: Tocilizumab was started at 390 mg/2 weeks (1st administration). Electrocardiogram was performed (immediately before and after initial dose). No abnormal findings were observed. The size of neck and axillary lymph nodes was 15 mm × 20 mm by palpation. 4 days after administration: Treatment was given by oral administration of prednisolone at 50 mg (until 6 days after administration). 6 days after administration: General malaise (PS: 3), anorexia, headache only at dawn were manifested. 7 days after administration: The patient received IV infusion of prednisolone sodium succinate, which was started at 50 mg and tapered by 5 mg to a maintenance dose of 30 mg (until 59 days after administration). 60 days of administration: Treatment was given by oral administration of prednisolone at 27 mg (until 66 days after administration). 67 days after administration: Treatment was given by oral administration of prednisolone at 25 mg (until 93 days after administration). 69 days after administration: Tocilizumab 400 mg was administered (the 6th administration). General malaise (PS: 3) and headache were manifested.	

				Around this time, clinical symptoms improved with improvement of anaemia. Lymph nodes were shrunk. The patient became able to take rehabilitation (200 m walking with caster and back support for instability of knee). 74 days after administration: After an assested bathing, the patient fell while getting out from the bathroom to the changing room and had fractures of right humerus and right femoral trochanter. The patient got a 3-cm open lesion on the left knee. She was transferred to another hospital to undergo invasive surgery of right femoral trochanter and hospitalized there. Her general condition became worse. 84 days after administration: Tocilizumab at 400 mg was started (the 7th administration). 94 days after administration: The patient had already developed pneumonia when transferred back to our hospital. She complained that she started to have pneumonia symptoms 2 days ago. KL-6 264 U/mL, β-D-glucan ≥300 pg/mL, pneumocystis carinii sputum PCR (–), CMV: negative. IVH was inserted after confirmation of pneumonia by CT. Treatment: infusion of micafungin sodium at 300 mg (for 1 week). The patient developed general malaise (PS: 4), blood cell decreased (serious), and received G-CSF. Treatment was given by IV infusion of prednisolone sodium succinate at 50 mg (until next day). 96 days after treatment: Treatment of pneumonia: Endotracheal intubation was conducted. KL-6 263 U/mL, β-D-glucan ≥300 pg/mL, and pneumocystis carinii sputum PCR: (–). Treatment was given by IV injection of prednisolone sodium succinate at 50 mg (until 98 days after administration) 97 days after administration: KL-6 181 U/mL, β-D-glucan ≥300pg/mL. 98 days after administration: Administration of tocilizumab had been scheduled this day, but was postponed due to an infectious disease. 99 days after administration: Treatment was given by IV infusion of prednisolone sodium succinate at 50 mg (until 108 days of administration).	

				101 days after administration: Since aggravation of the primary disease was suggested based on the IL-6 of 77800 pg/mL on 94 days after administration and improvement of infection was confirmed by laboratory findings, tocilizumab was administered at 400 mg (the 8th administration). General malaise (PS: 4), pyrexia, night sweats, anorexia, chills, wheezing, and cough occurred. Voriconazole at 200 mg was administered intravenously for the treatment of pneumonia (for 1 week). KL-6 180 U/mL, β-D-glucan ≥300 pg/mL, pneumocystis carinii sputum PCR: (−). 105 days after administration: β-D-glucan ≥300 pg/mL, pneumocystis carinii sputum PCR: (−). 106 days after administration: Aspergillus was detected in sputum. 107 days after administration: White blood cell decreased was improved. 109 days after administration: The general condition was further aggravated. The patient developed multi-organ failure, and she died of pneumonia.	
	Concomitant medications: prednisolone sodium succinate, prednisolone, insulin, alendronate sodium hydrate, sulfamethoxazole/trimethoprim				

Clinical Laboratory Values

	74 days before administration	1 day before administration	6 days after administration	12 days after administration	41 days after administration	55 days after administration	69 days after administration	81 days after administration	88 days after administration
WBC (/mm^3)	--	11440	15260	11130	7960	8400	10170	8700	4900
Neutrophils (%)	--	80	84	78	57	70	71	--	--
Hb (g/dL)	--	10.6	11.4	12.6	10.9	11.7	12.8	7.9	9.9
Platelet count (×10^4/mm^3)	--	15.6	12.9	10.1	8.5	7.9	7.6	8.3	6.0
CRP (mg/dL)	--	2.16	0.13	0.12	0.04	0.04	0.03	0.06	0.03
IL-6 (pg/mL)	8.7	--	--	219	--	--	--	--	--

	94 days after administration	95 days after administration	98 days after administration	100 days after administration	101 days after administration	103 days after administration	107 days after administration	108 days after administration
WBC (/mm^3)	1420	1280	1140	1760	3050	1850	3890	3980
Neutrophils (%)	13.5	27	45	26.2	28	13	--	35
Hb (g/dL)	11.9	9.4	7.3	7.4	7.3	6.8	7.7	7.4
Platelet count (×10^4/mm^3)	4.7	5.3	5	4.1	3.6	5.4	4.3	2.9
CRP (mg/dL)	4.79	10.78	2.25	0.97	10.73	6.05	3.73	5.17
IL-6 (pg/mL)	77800	--	--	--	13500	--	--	--

WBC: White Blood Cell Hb: Haemoglobin
CRP: C-Reactive Protein IL-6: Interleukin 6

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	Remarks
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
2	Female 30s	Castleman's disease (interstitial pneumonia)	480 mg 126 days (9 times) 500 mg 28 days (twice) 520 mg 33 days (twice) 560 mg 120 days (9 times)	**Pneumonia bacterial** Approx. 9 months before administration: The patient was diagnosed with Castleman's disease (plasma cell type). Associated symptoms: interstitial pneumonia 203 days before administration: CT was performed to confirm swollen lymph nodes. Sites of swollen lymph nodes: neck, abdomen, axilla Groin: short axis (10 mm), long axis (10 mm) (both neck and axilla) Approx. 108 days before administration: Oral administration of prednisolone at 15 mg was started for the treatment of Castleman's disease. Azathioprine at 50 mg was also started (and continued for approximately 4 months). 20 days before administration: The dose of prednisolone was increased to 30 mg. On day 1 of administration: Tocilizumab was administered at 480 mg (the 1st administration). Pyrexia, night seats, and anorexia were noted. General malaise (PS: 1) Plain roentgenography was performed for interstitial pneumonia. Physical observations: cough Electrocardiogram was performed (immediately before and after initial dose). No abnormal findings were observed. 14 days after administration: Tocilizumab was administered at 480 mg (2nd administration). General malaise (PS: 0) without symptoms. Prednisolone was continued with gradual reduction of dose until the 9th administration. 126 days after administration: The dose of tocilizmub was increased to 500 mg (the 10th administration). The patient was on prednisolone at 12 mg. 154 days after administration: The dose of tocilizmub was increased to 520 mg (the 12th administration). The patient was on prednisolone 9 mg. 173 days after administration: Tocilizmub was administered at 520 mg (the 13th administration). The patient was on prednisolone at 8 mg. CT was performed to confirm swollen lymph nodes. Sites of swollen lymph nodes: neck, abdomen, groin, axilla Findings: swollen lymph nodes were decreased on abdomen and unchanged on groin. High resolution CT was performed for interstitial pneumonia.	Company report

				Degree of improvement: improved 187 days after administration: The dose of tocilizmub was increased to 560 mg (the 14th administration). The patient was on prednisolone at 7 mg. 285 days after administration: Tocilizmub was administered at 560 mg (the 21st administration). The patient was on prednisolone at 1 mg. 299 days after administration: The patient had only slight elevation of CRP and no pyrexia, but she had symptoms of cough. Examinations such as imaging were performed and confirmed pneumonia bacterial. She was hospitalized. Chest CT findings: infiltrative shadow with air bronchogram was observed in the right S9. Chest X-ray findings: infiltrative shadow in the lower lobe of right lung. Urinary pneumococcal antigen test: negative Sputum culture: normal flora Treatment: imipenem/cilastatin sodium at 0.5 g b.i.d. (for 2 weeks), Administration of tocilizumab was postponed. General malaise (PS: 1) Associated symptoms: anorexia On the same day, swollen lymph nodes (neck, abdomen, chest, and pelvis) were confirmed by CT. Findings: short axis (10 mm), long axis (10 mm) (no marked changes in lymph nodes of supraclavicular fossa, axilla, mediastinum) 300 days after administration: Clarithromycin at 200 mg b.i.d. was added (for 13 days) for the treatment of pneumonia bacterial. 306 days after administration: Tocilizmub was administered at 560 mg (the 22nd administration). Cough was noted. 312 days after administration: Chest X-ray findings: The infiltrative shadow in the lower lobe of right lung disappeared. The pneumonia bacterial was improved.	
	Concomitant medications: prednisolone, azathioprine				

Clinical Laboratory Values

	271 days after administration	285 days after administration	299 days after administration	306 days after administration	312 days after administration
WBC (/mm^3)	6700	6600	4800	8100	7400
Neutrophils (%)	51.8	53.5	47.4	66.5	63.2
Lymphocytes (%)	27.0	27.4	36.4	17.0	22.3
CRP (mg/dL)	0.1	0.1	0.4	0.3	0 1

WBC: White Blood Cell
CRP: C-Reactive Protein

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Revision of PRECAUTIONS (No. 183)

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 December 1, 2006 (excluding those presented in "1. Important Safety Information" of this Bulletin), together with reference information.

1 <Anticoagulants> Danaparoid Sodium

[Brand Name] Orgaran Injection (Nippon Organon K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Haemorrhage:** Serious haemorrhage such as haemorrhage of digestive tract may occur. Patient should be carefully monitored. If any abnormalities are observed, appropriate measures, such as reducing the dose and discontinuing the drug, should be taken.

<Reference Information> Company report

2 <Miscellaneous metabolism agents> Gabexate Mesilate

[Brand Name] FOY 100 and 500 for Injection (Ono Pharmaceutical Co., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Agranulocytosis, leucopenia, thrombocytopenia:** Agranulocytosis, leucopenia, thrombocytopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued.

<Reference Information> Company report

3 <Antineoplastics-Antibiotics, Non-main therapeutic purpose agents-Miscellaneous> Zinostatin Stimalamer Iodine Addition Products of the Ethylesters of the Fatty Acids Obtained From Poppyseed Oil (suspension vehicle)

[Brand Name] Smancs 4 mg and 6 mg for Hepatic Intra-arterial Injection (Astellas Pharma Inc.)
Smancs Suspension Vehicle 4 mL and 6 mL for Hepatic Intra-arterial Injection (Astellas Pharma Inc.)

[Warning]

WARNING

Serious adverse reactions, such as shock, hepatic failure, acute renal failure, gastric perforation, and gastrointestinal haemorrhages/ulceration,may occur. This product should be prescribed in facilities equipped with adequate supportive medical resources in case of emergency and by physicians who have sufficient knowledge and experience with this therapy.

[Important Precautions] Entry of this drug into untargeted sites may induce serious adverse reactions, such as gastric perforation, gastrointestinal haemorrhages, gastric and/or duodenal ulcers, cerebral infarction, pulmonary infarction, pulmonary embolism, adult respiratory distress syndrome, and spinal cord infarction. The following cautions should be exercised when administering this product.

[Adverse Reactions **Gastric perforation, gastrointestinal haemorrhages/ulceration:** Gastric

(clinically significant adverse reactions)]	perforation, gastrointestinal haemorrhages/ulcerationt, gastric and/or duodenal ulcers, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken.
<Reference Information>	Company report

<Biological preparations-Miscellaneous>

4 Peginterferon Alfa-2a (Genetical recombination)

[Brand Name]	Pegasys s.c. 90 μg and 180 μg (Chugai Pharmaceutical Co., Ltd.)
[Adverse Reactions (clinically significant adverse reactions)]	**Haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP):** Haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), with platelets decreased, anaemia and renal failure as major symptoms, may occur. Patient should be carefully monitored through periodic blood test (platelet count, red blood cell count etc.) and renal function test. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.
<Reference Information>	Company report

3

List of products subject to Early Post-marketing Phase Vigilance

(As of January 1, 2007)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Sertraline Hydrochloride / Jzoloft Tablets 25 mg and 50 mg	Pfizer Japan Inc.	July 7, 2006
Somatropin (Genetical recombination) / Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg[*1]	Pfizer Japan Inc.	July 26, 2006
Inulin / Inulead Inj.	FUJIYAKUHIN Co., Ltd.	August 22, 2006
Alendronate Sodium Hydrate / Fosamac Tablets 35 mg	Banyu Pharmaceutical Co., Ltd.	September 15, 2006
Alendronate Sodium Hydrate / Bonalon Tablet 35 mg	Teijin Pharma Limited	September 15, 2006
Itraconazole / Itrizole Oral Solution 1%	Janssen Pharmaceutical K.K.	September 15, 2006
Temozolomide / Temodal Capsules 20 mg and 100 mg	Schering-Plough K.K.	September 15, 2006
Budesonide / Pulmicort Respules 0.25 mg and 0.5 mg	AstraZeneca K.K.	September 15, 2006
Entecavir Hydrate / Baraclude Tablets 0.5 mg	Bristol Pharmaceuticals Y.K.	September 21, 2006
Cetrorelix Acetate / Cetrotide for Injection 0.25 mg and 3 mg	Nippon Kayaku Co., Ltd.	September 21, 2006
Manganese Chloride Tetrahydrate / Bothdel Oral Solution 10	Meiji Dairies Corporation	September 25, 2006
Gabapentin / Gabapen Tablets 200 mg, 300 mg, and 400 mg	Pfizer Japan Inc.	September 25, 2006
Olopatadine Hydrochloride / Patanol Ophthalmic Solution 0.1%	Alcon Japan Ltd.	October 5, 2006
Busulfan / Busulfex Injection 60 mg	Kirin Brewery Company, Limited	October 10, 2006[*2] / October 20, 2006[*3]
Fexofenadine Hydrochloride / Allegra Tablets 60 mg[*4]	Sanofi-Aventis K.K.	October 20, 2006
Landiolol Hydrochloride / Onoact 50 for Injection	Ono Pharmaceutical Co., Ltd.	October 20, 2006
Mozavaptan Hydrochloride / Physuline Tablets 30 mg	Otsuka Pharmaceutical Co., Ltd.	October 24, 2006
Interferon Beta-1a (Genetical recombination) / Avonex IM Injection Syringe 30 μg	Biogen Idec Japan Ltd.	November 6, 2006

Moxifloxacin Hydrochloride Vegamox Ophthalmic Solution 0.5%	Alcon Japan Ltd.	November 6, 2006
Pneumococcal Vaccine Pneumovax NP	Banyu Pharmaceutical Co., Ltd.	November 29, 2006
Bortezomib Velcade Injection 3 mg	Janssen Pharmaceutical K.K.	December 1, 2006
Itraconazole Itrizole Injection 1%	Janssen Pharmaceutical K.K.	December 6, 2006
Ropinirole Hydrochloride ReQuip Tablets 0.25 mg, 1 mg, and 2 mg	GlaxoSmithKline K.K.	December 6, 2006
Lansoprazole Takepron Intravenous 30 mg	Takeda Pharmaceutical Company Limited	December 7, 2006
Losartan Potassium/Hydrochlorothiazide Preminent Tablets	Banyu Pharmaceutical Co., Ltd.	December 8, 2006
Polidocanol Polidocasklerol 0.5%, 1%, and 3% Inj. 2 mL	Sakai Chemical Industry Co., Ltd.	December 14, 2006

*1: An additional indication for “adult growth hormone hyposecretion (for severe cases only)”
*2: For the adult dose initially approved
*3: An additional administration for “pediatrics”
*4: An additional administration for “pediatrics (aged 7 and older)”