Pharmaceuticals and Medical Devices Safety Information

No. 249 August 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. 249 August 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.

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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 July 4, 2008.

1 Tiotropium Bromide Hydrate

Brand Name (name of company)	Spiriva Inhalation Capsules 18 μg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic Category	Respiratory organ agents-Bronchodilators
Indications	Remission of various symptoms associated with airway obstructive disturbances in chronic obstructive pulmonary disease (COPD), (including chronic bronchitis and emphysema).

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

[Adverse Reactions (clinically significant adverse reactions)]

Ileus: Ileus may occur. If abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2005 to May 23, 2008) (events for which a causality to the drug could not be denied)

- Ileus: 4 cases (no fatal case)

The number of patients treated with Tiotropium for a year estimated by MAH (Marketing Authorisation Holder): approximately 180000 (January to December 2007)

Marketed in Japan in: December 2004

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 80s	Emphysema (asthma)	18 μg 493 days	**Ileus** On day 1 of administration: Inhalation of this drug was started. On day 476 of administration: Abdominal distension occurred. Ileus developed. On day 477 of administration: Abdominal distension was (2+). The patient was examined at a department of surgery and ileus was confirmed by X-ray. He was hospitalized for treatment. An ileus tube was inserted. Administration of sodium chloride/potassium chloride/sodium lactate/glucose electrolyte solution (maintenance fluid) at 1000 mL for 1 day, acetated Ringer's solution at 500 mL for 2 days, and cefotiam hydrochloride at 2 g for 2 days, was conducted.

				On day 478 of administration: Glucose-added acetic acid maintenance solution at 1000 mL was administrated for 9 days. On day 483 of administration: As improvement was confirmed by contrast radiography, the tube was removed. On day 484 of administration: The patient started eating without any particular problem. On day 486 of administration: The patient was discharged from the hospital. Administration of this drug was continued. On day 494 of administration (day of discontinuation): The patient was rehospitalized due to recurrent ileus. Administration of this drug was discontinued. An ileus tube was inserted. Administration of glucose added acetated Ringer's solution, glucose-added acetic acid maintenance solution and sodium chloride/potassium chloride/sodium lactate/ multiple electrolyte maintenance solution with glucose (maintenance solution) at a total of 2000 mL for 15 days, metoclopramide at 10 mg for 15 days, and panthenol at 500 mg for 15 days, was conducted. 6 days after discontinuation: The ileus tube was removed. 21 days after discontinuation: The patient was recovered and discharged from the hospital.
	Concomitant medications: beclometasone dipropionate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Gender/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Emphysema (hyperuricaemia)	18 μg 180 days	**Ileus** On day 1 of administration: Inhalation of this drug was started. On day 180 of administration (day of discontinuation): Abdominal discomfort developed at night. The patient tended to be constipated. Ileus developed. Inhalation of this drug was discontinued. 4 days after discontinuation: The patient felt queasy after lunch. He vomited residual gastric contents. The patient was examined in the emergency room of our hospital. Abdominal distension and decreased bowel sounds were detected. Since a plain abdominal X-ray showed massive gastric contents retained and large amount of faecal masses as well as an image of small intestinal gas, the patient was hospitalized. The patient had a bowel movement following glycerin enema in the evening. Abdominal discomfort was in remission. Bowel sounds could be slightly heard. 5 days after discontinuation: In the morning, displacement of small intestinal gas was confirmed by plain abdominal X-ray. Queasy and abdominal distension were further improved. 6 days after discontinuation: Although the patient resumed eating in the morning, he had no abdominal symptoms.

				9 days after discontinuation: Upper gastrointestinal endoscopy in the evening revealed no lesion that could cause ileus. 13 days after discontinuation: Lower gastrointestinal endoscopy in the daytime revealed no lesion that could cause ileus. 17 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: salmeterol xinafoate, allopurinol			

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Revision of PRECAUTIONS (No. 199)

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 July 4, 2008 (excluding those presented in "1. Important Safety Information" of this Bulletin).

1 <Stimulation therapy agents> Bucillamine

[Brand Name] Rimatil tablets 50 mg and 100 mg (Santen Pharmaceutical Co., Ltd.) and others

[Contraindications] Patients with a history of hypersensitivity to ingredients of this drug

[Adverse Reactions (clinically significant adverse reactions)] **Shock, anaphylactoid symptoms:** Shock, anaphylactoid symptoms may occur. Patients should be carefully monitored, and if symptoms such as erythema, rash, vomiting, dyspnoea, blood pressure decreased are observed, administration should be discontinued and appropriate measures should be taken.

2 <Antivirals> Darunavir Ethanolate

[Brand Name] Prezista Tablets 300 mg (Janssen Pharmaceutical K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder, jaundice:** Hepatic function disorder with an increase in AST (GOT), ALT (GPT), γ-GTP levels, etc. and jaundice may occur. Patients should be carefully monitored through periodic liver function test etc. If any abnormalities are observed, appropriate measures, such as discontinuing treatment, should be taken.

3 <Non-main therapeutic purpose agents-Miscellaneous> Varenicline Tartrate

[Brand Name] CHAMPIX Tablets 0.5 mg and 1 mg (Pfizer Japan Inc.)

[Important Precautions] Smoking cessation with or without treatment has been reported to be associated with various symptoms (discomfort, depressed mood, insomnia, bad mood, frustration, anger, anxiety, concentration difficulty, restlessness, heart rate decreased, increased appetite, weight increased, etc.). These symptoms may worsen underlying mental conditions. It has also been reported that depressed mood, anxiety, irritation, excitement, changes in behaviour, suicidal ideation, and suicide occurred in patients who had attempted to quit smoking with this drug, although the causality to this drug is unknown. Patients administered with this drug should be carefully monitored. Patients should also be instructed to stop taking this drug and contact a physician etc. immediately if such symptoms and/or behaviour occur.

4 Over the counter drugs Product Containing Dextromethorphan Hydrobromide or Dextromethorphan Phenolphthalinate

[When not to use the product]

This product should not be used in the following persons.
People who have had allergic symptoms in relation to this drug.

[Consultation]

In case of the following, immediately discontinue administration and bring this document to your doctor or pharmacist for consultation.
If the following symptoms are observed after taking this drug
In rare instances, the following serious symptoms may occur. Visit a physician immediately in such a case.
Shock (anaphylaxis): Immediately after administration, urticaria, oedema, chest distress, etc. may occur concurrently with pallor facial, cold hands and feet, cold sweat and respiratory discomfort.

Over the counter drugs

5 Cold Medicine (internal use) [preparations with the indication for patients under 2 years of age (preparations with the indication for patients under a year of age)]
Antitussive and Expectorant (internal use) [preparations with the indication for patients under 2 years of age (preparations with the indication for patients under a year of age)]
Medicine for Rhinitis [preparations with the indication for patients under 2 years of age (preparations with the indication for patients under a year of age]

[Precautions of Dosage and Administration]

For infants under 2 years of age, examination by a physician should always precede administration of this drug. This drug should be administered only if it is absolutely necessary.

(Note) "For infants under 2 years of age, examination by a physician should always precede administration of this drug. This drug should be administered only if it is absolutely necessary" should be described on an outer container and a wrapper of the product.

Over the counter drugs

6 Cold Medicine (internal use) [preparations with the indication for patients under 2 years of age (preparations without the indication for patients under a year of age)]
Antitussive and Expectorant (internal use) [preparations with the indication for patients under 2 years of age (preparations without the indication for patients under a year of age)]
Medicine for Rhinitis [preparations with the indication for patients under 2 years of age (preparations without the indication for patients under a year of age)]

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List of products subject to Early Post-marketing Phase Vigilance

(As of August 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 10mg/2mL*4	Daiichi Sankyo Co., Ltd.	July 16, 2008
Argatroban Hydrate Novastan HI inj. 10mg/2mL*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 17.5mg*6	Takeda Pharmaceutical Company Limited	July 16, 2008
Diazoxide Aroglycem Capsules 25 mg	Schering-Plough K.K.	July 22, 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"