Pharmaceuticals and Medical Devices Safety Information

No. 247 June 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. 247 June 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

Revision of PRECAUTIONS (No. 197)

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 April 25, 2008.

1 <Antiepileptics> Carbamazepine

[Brand Name] Tegretol Fine Granules 50%, Tegretol Tablets 100 mg and 200 mg (Novartis Pharma K.K.) and others

[Adverse Reactions (clinically significant adverse reactions)]

Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (dermatitis exfoliative): Since serious skin symptoms may occur, patients should be carefully observed. If abnormalities including pyrexia, ocular hyperaemia, swelling face, lip·oral mucosa erosion, vulvar erosion, skin blister, mucosa blister, erythemas, pain pharynx, pruritus and general malaise are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.
Since most of these symptoms appear within 3 months after the initiation of administration, patients should be carefully observed, especially during the initial administration period.

[Other Precautions]

Retrospective studies in patients of Han Chinese ancestry have found that in almost all cases, patients with oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) associated with carbamazepine were carriers of HLA-B*1502 allele. The prevalence of carriers of HLA-B*1502 allele appears to be above 15% of the population in the Philippines, Thailand, Hong Kong and Malaysia, around 10% in Taiwan and less than 1% in Japan and Korea. The correlation between oculomucocutaneous syndrome/toxic epidermal necrolysis and Japanese carriers of HLA-B*1502 allele is unknown.

<Reference Information>

Chung, W.H., et al.: Nature 2004; 428 (6982): 486
Hung, S.I., et al.: Pharmacogenetics and Genomics 2006; 16 : 297-306

2 <Antiparkinsonian agents> Bromocriptine Mesylate

[Brand Name] Parlodel 2.5 mg (Novartis Pharma K.K.) and others

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac valvulopathy: Since cardiac valvulopathy may occur, patients should be carefully monitored. If development and/or aggravation of cardiac murmur is observed, chest X-ray examination or echocardiography etc. should be promptly performed. If cardiac valve leaflet thickening , cardiac valve motion restriction or associated cardiac valve lesion such as stenosis are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Gastrointestinal haemorrhage, gastric and/or duodenal ulcers: Gastrointestinal haemorrhage, gastric and/or duodenal ulcers may develop or gastric and/or duodenal ulcers may be exacerbated during therapy with this drug. If such events occur, administration of this drug should be discontinued and appropriate measures should be taken.

<Skeletal muscle relaxants>

3 Chlorphenesin Carbamate

[Brand Name]

Rinlaxer Tab. 125 mg and 250 mg (Taisho Pharmaceutical Co., Ltd) and others

[Adverse Reactions (clinically significant adverse reactions)]

Toxic epidermal necrolysis (Lyell syndrome): Toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

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

4 Doripenem Hydrate

[Brand Name]

Finibax 0.25g IV Solution, Finibax 0.25g IV Solution Kit (Shionogi & Co., Ltd)

[Adverse Reactions (clinically significant adverse reactions)]

Agranulocytosis, leukopenia: Agranulocytosis, leukopenia may occur. Patients should be carefully monitored through periodical blood test etc. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

2

List of products subject to Early Post-marketing Phase Vigilance

(As of June 1, 2008)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
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. 1 mg	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*[1]	Kyorin Pharmaceutical Co., Ltd.	January 25, 2008
Montelukast Sodium Singulair Tablets-10*[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	AnGens 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

*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”

Reference Material

Information on Heparin Sodium Products etc.

The brief summary of the results of the investigation on “heparin sodium products etc.” by the Subcommittee of the Committee on Drug Safety under the Pharmaceutical Affairs and Food Sanitation Council (held on April 22, 2008) is presented. Please refer to the “full text” of the results of the investigation and reference materials from the Subcommittee on Drug Safety available on the MHLW website (http: //www.mhlw.go.jp/) in Japanese, as well.

April 22, 2008
Subcommittee on Drug Safety
Committee on Drug Safety
Pharmaceutical Affairs and
Food Sanitation Council

Information on Heparin Sodium Products etc.

The subcommittee was informed that the increased occurrence of adverse reactions associated with "heparin sodium products etc." had not been observed in Japan and that contaminants (over-sulfated chondroitin sulfate) had not yet been identified in purified heparin used for these products shipped in Japan.

"Heparin sodium products etc." include heparin calcium products, dalteparin sodium products, parnaparin sodium products, reviparin sodium products and enoxaparin sodium products.

At present, the cause of the increased occurrence of adverse reactions such as allergies in the United States and other countries is unknown. However, reflecting that heparin sodium products etc. are therapeutically important products used for life-saving purposes, this subcommittee considers that it is appropriate to take the following measures for heparin sodium products etc. for the time being.

1. Strengthening of Quality Control

(1) The MHLW should remind marketing authorisation holders of heparin sodium products etc. to follow the procedures below in order to ensure thorough quality control of these products:

a. The marketing authorisation holders must conduct immediate inspection to determine if their products and raw materials have any problems regarding safety assurance by validating that manufacturing processes are carried out under the control of good manufacturing and quality.

b. When manufacturing heparin sodium products etc., the marketing authorisation holders must conduct an appropriate test for each lot to ensure that purified heparin etc. used as raw materials are contaminant-free by using a test method published by the Food and Drug Administration as a reference for the time being, in addition to performing validation of provisions set forth in an approval document etc.

(2) The MHLW should provide the marketing authorisation holders with an appropriate guidance for the test method in (1) b. with the assistance of the National Institute of Health Sciences, in cooperation with US and European regulatory authorities.

2. Reinforcement of Collection/Provision of Safety Information

The MHLW should remind the marketing authorisation holders to alert healthcare providers by providing the following information and collect the information associated with adverse reactions regarding heparin sodium products etc. validated by the above 1 (1) b. The MHLW also should make an effort to remind healthcare providers of the alert in cooperation with relevant associations and societies as well.

- **Heparin sodium products etc. should be used with enough caution against adverse reactions such as shock described in "the clinically significant adverse reaction" section of the package inserts. Patients should be carefully monitored for signs of anaphylactic symptoms such as decreased blood pressure or decreased consciousness during and immediately after the use of these products.**
- **Most of adverse reactions reported in the United States have been associated with high doses (5,000 - 50,000 units) of bolus administration (a method for intravenously administering a drug at high dose in a short time period to cause more rapid onset of effects). Caution should be exercised against dose and infusion rate when using heparin sodium products etc.**

3. The MHLW should continue its efforts to collect information regarding the quality and safety of heparin sodium products etc. from national and international sources, and take prompt and appropriate measures when necessary.