Pharmaceuticals and Medical Devices Safety Information

No. 257 May 2009

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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. 257 May 2009

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

To Pharmaceuticals and Medical Devices Safety Management Supervisor
—Please use our e-mail alert service—

Pharmaceuticals and Medical Devices Agency is providing a "Pharmaceuticals and Medical Devices Information E-mail Alert Service" (http://www.info.pmda.go.jp/info/idx-push.html, Japanese only), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of PRECAUTIONS is issued. You are encouraged to register to and use the service.

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

Implementation of appropriate management/maintenance of automated external defibrillators (AEDs)

1. Outline

An automated external defibrillator (AED) is a medical device that automatically analyzes electrocardiograms, determines whether to provide an electrical shock for defibrillation. It notifies the user when a shock should be given, and performs the defibrillation by pressing a button manually. In Japan, AEDs are becoming increasingly prevalent not only at medical institutions, but at schools, stations, and other public and commercial facilities since the handling of AEDs by general public at scenes of life-threatening emergency was presented by HPB Notification No. 0701001 of Secretary-General of Health Policy Bureau, MHLW, dated July 1, 2004, "Use of Automated External Defibrillators by Non-healthcare Professionals".

However, being classified by the Pharmaceutical Affairs Law as specially controlled medical device and designated maintenance and management required medical device, an AED may have significant adverse effect on human life and health if not managed properly.

In view of the above, strengthening the appropriate management and maintenance of AEDs, MHLW compiled issues requested AED installation personnel to remind and inform the relevant organizations for all prefectural governors on April 16, 2009. MHLW also notified AED manufacturers to provide AEDs installation personnel with resources and any other relevant information necessary to implement these measures.

2. Issues Requested AEDs installation personnel

(1) Implementation of daily checks, etc.

AEDs installation personnel (individuals responsible for the installment and management of AEDs, including facility managers) are requested to allocate AED inspection coordinators responsible for the following daily checks, etc.

- Day-to-day to check and record of the AED indicator display.
- To check the display label for exchange dates of consumables (electrode pads and batteries) and their appropriate exchange.

* Labels are provided by each AED manufacturers through shops where AEDs are purchased.

Figure - Example label

< Description on label >

Exchange date for electrode pads for adult use
December, 2010

Exchange date for electrode pads for pediatric use
December, 2010

Exchange date for batteries (approximate)
April, 2011

* The battery expiration date can change depending on environment and usage of the installed AED.

(2) Registration of information on installation of AEDs

AEDs installation personnel is encouraged to share and thoroughly provide the information on AED locations, and to register information on the installation of an AEDs to enable AED manufacturers to promptly provide safety information (recall information) on their AEDs. The Registered information on a basis of non-disclosure is also available.

For information on the registration procedure, please contact the shop purchased the AED, or the manufacturer.

(Reference information) [In Japanese]
Website of AED locations (Japan Foundation for Emergency Medicine)
http://www.qqzaidan.jp/AED/aed.htm

3. Contact Addresses for AED manufacturer

- ○ MBS Co., Ltd. (Distributor: Daewoo International Japan Corp.)
  Product name: Paramedic
  Phone: 0120-915-256 or 03-3224-7143 (Daewoo International Japan Corp.)
  Website: http://japan.daewoo.com/index.jsp
- ○ Nihon Kohden Corporation
  Product name: cardiolife
  Phone: 0120-233-821 (AED maintenance contact center)
  Website: http://www.nihonkohden.co.jp/aed/
- ○ Medtronic Inc.
  Product name: LIFEPAK
  Phone: 0120-715-545 (LIFEPAK customer center)
  Website: http://www.medtronic-lifepak.com/
- ○ Phillips Electronics Japan, Ltd.
  Product name: HEARTSTART
  Phone: 0120-802-337 (AED call center)
  Website: http://www.philips.co.jp/

4. Closing Comments

For further information on these matters, please access the MHLW website (http://www.mhlw.go.jp/) [in Japanese] which provides relevant notifications, easy-to-understand material based on these measures entitled “Are you checking AED?,” FAQs, a list of AEDs product aspect, and a list of major facilities installed AEDs.

You are encouraged to ensure good management of AEDs for their proper application in emergencies.

2

Revision of PRECAUTIONS

(No. 205)

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 March 19, 2009.

<Antipyretics and analgesics, anti-inflammatory agents>

1 Naproxen

[Brand Name] NAIXAN Tablets 100mg, NAIXAN Capsules 300mg
(Mitsubishi Tanabe Pharma Corporation)

[Contraindications] Women late in their pregnancy

<Antipyretics and analgesics, anti-inflammatory agents >

2 Bucolome

[Brand Name] PARAMIDIN CAPSULES 300mg
(ASKA Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome):** Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be closely monitored, and if such abnormalities are observed, administration of this drug should be immediately discontinued and appropriate measures should be taken.

<Antiparkinsonian agents>

3 Entacapone

[Brand Name] Comtan Tablets 100 mg
(Novartis Pharma K.K.)

[Important Precautions] In the case of concomitant therapy with this drug and levodopa, impulse-control disorders such as pathological gambling (a state of continuous gambling despite bringing about socially detrimental results such as the destruction of the individual's life), increased libido and hypersexuality have been reported as well as in patients with Parkinson's disease receiving levodopa or dopamine receptor agonist. If such symptoms are observed, appropriate measures such as reducing or discontinuing administration should be taken.

<Antihypertensives>

4 Telmisartan

[Brand Name] Micardis Tablets 20 mg and 40 mg
(Nippon Boehringer Ingelheim Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Anaphylactoid symptoms:** Symptoms such a dyspnoea, blood pressure decreased, and laryngeal oedema may occur. Patients should be closely monitored and if such abnormalities are observed, administration should be immediately discontinued and appropriate measures should be taken.

5 <Antihypertensives>
Losartan potassium/Hydrochlorothiazide

[Brand Name]

PREMINENT Tablets
(Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)]

Acute renal failure: Acute renal failure may occur. Patients should be closely monitored. If any abnormalities are observed, appropriate measures should be immediately taken.

Hyponatremia: Hyponatremia accompanying malaise, anorexia, queasy, vomiting and consciousness disturbed may occur (particularly in the elderly). Patients should be closely monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be immediately taken.

6 < Antineoplastics -Miscellaneous >
Exemestane

[Brand Name]

Aromasin Tablets 25 mg (Pfizer Japan Inc.)

[Adverse Reactions (clinically significant adverse reactions)]

Hepatitis, hepatic function disorder, jaundice: Hepatic function disorder with elevations of AST(GOT) , ALT(GPT), Al-P and γ -GTP, or jaundice may occur. Patients should be closely monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

7 <Acting mainly on mold>
Voriconazole

[Brand Name]

VFEND Tablets 50mg and 200mg, VFEND for Intravenous Use
(Pfizer Japan Inc.)

[Warning]

WARNING

Symptoms including photophobia, vision blurred or vision disorder may occur and become persistent after discontinued this product. Patients should be advised to refrain from engaging in potentially hazardous operations including driving, until recovery from such symptoms during or after treatment with this drug.

[Important Precautions]

Eye disorders with optic neuritis or papilloedema may occur, and symptoms including photophobia, vision blurred or vision disorder may become persistent after discontinued this product. Before commencing treatment with this product, patients should be informed about such symptoms, and be advised to see ophthalmology specialist if necessary.

[Adverse Reactions (clinically significant adverse reactions)]

Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feeling of weakness, CK (CPK) increased, and blood myoglobin increased and urine myoglobin increased may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

8 <Antivirals>
Entecavir Hydrate

[Brand Name]

Baraclude Tablets 0.5 mg (Bristol-Myers K.K.)

[Adverse Reactions (clinically significant adverse reactions)]

Anaphylactoid symptoms: Anaphylactoid symptoms may occur. Patients should be carefully monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

3

List of products subject to Early Post-marketing Phase Vigilance

(As of May 1, 2009)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Anti-human Thymocyte Immunoglobulin, Rabbit / Thymoglobuline for Intravenous Infusion 25 mg	Genzyme Japan K.K.	November 28, 2008
Pirfenidone / Pirespa Tablets 200 mg	Shionogi & Co., Ltd.	December 12, 2008
Lamotrigine / Lamictal Tablets 2 mg, 5 mg, 25 mg, and 100 mg	GlaxoSmithKline K.K.	December 12, 2008
Tafluprost / TAPROS ophthalmic solution 0.0015%	Santen Pharmaceutical Co., Ltd.	December 16, 2008
Phenobarbital Sodium / NOBELBAR 250 mg for Injection	Nobelpharma Co., Ltd.	December 16, 2008
Haemophilus influenzae type b conjugate vaccine / ActHIB	Sanofi Pasteur-Daiichi Sankyo Vaccine Co., Ltd.	December 19, 2008
Thyrotropin Human Alfa (genetical recombination) / THYROGEN IM Injection 0.9 mg	Sato Pharmaceutical Co., Ltd.	January 13, 2009
Etravirine / INTELENCE Tablets 100 mg	Janssen Pharmaceutical K.K.	January 19, 2009
Salmeterol Xinafoate/Fluticasone Propionate / Adoair 100 Diskus *1	GlaxoSmithKline K.K.	January 21, 2009
Salmeterol Xinafoate/Fluticasone Propionate / Adoair 250 Diskus *2	GlaxoSmithKline K.K.	January 21, 2009
Ganirelix Acetate / Ganirest Subcutaneous 0.25mg Syringe	Schering-Plough K.K.	January 22, 2009
Maraviroc / CELSENTRI Tablets 150 mg	Pfizer Japan Inc.	January 22, 2009
Dasatinib Hydrate / SPRYCEL Tablets 20 mg and 50 mg	Bristol Myers K.K.	February 2, 2009
Estradiol·Norethisterone Acetate / MENOAID COMBIPATCH	ASKA Pharmaceutical Co., Ltd.	February 5, 2009
Thalidomide / THALED capsule 100	Fujimoto Pharmaceutical Corporation	February 6, 2009
Nilotinib Hydrochloride Hydrate / TASIGNA Capsules 200 mg	Novartis Pharma K.K.	February 16, 2009
Estradiol·Levonorgestrel / Wellnara	Bayer Yakuhin, Ltd.	February 17, 2009
Botulinum toxin type A / BOTOX Vista Injection 50 Units	GlaxoSmithKline K.K.	February 23, 2009

Enoxaparin Sodium Clexane for Subcutaneous Injection Kit 2000 IU [*3]	Sanofi-Aventis K.K.	February 23, 2009
Lanthanum Carbonate Hydrate Fosrenol Chewable Tablets 250mg and 500mg	Bayer Yakuhin, Ltd.	March 11, 2009
Omalizumab（Genetical Recombination） Xolair for s.c. injection	Novartis Pharma K.K.	March 13, 2009
Candesartan Cilexetil / Hydrochlorothiazide ECARD Combination Tablets LD, ECARD Combination Tablets HD	Takeda Pharmaceutical Company Limited	March 13, 2009
Zonisamide TRERIEF Tablets 25mg	Dainippon Sumitomo Pharma Co., Ltd.	March 13, 2009
Valsartan/Hydrochlorothiazide Co-DIO Combination Tablets MD, Co-DIO Combination Tablets EX	Novartis Pharma K.K.	March 13, 2009
Ranibizumab（Genetical Recombination） LUCENTIS solution for intravitreal injection 2.3mg/0.23mL	Novartis Pharma K.K.	March 13, 2009
Nalfurafine Hydrochloride REMITCH CAPSULES 2.5μg	Toray Industries, Inc.	March 24, 2009
Azithromycin Hydrate ZITHROMAC SR Dry Syrup 2g for Adults	Pfizer Japan Inc.	April 6, 2009
Salmeterol Xinafoate/Fluticasone Propionate Adoair 50 Air 120 puffs	GlaxoSmithKline K.K.	April 6, 2009
Minodronic Acid Hydrate Bonoteo Tablets 1mg	Astellas Pharma Inc.	April 7, 2009
Minodronic Acid Hydrate RECALBON Tablets 1mg	Ono Pharmaceutical Co., Ltd.	April 7, 2009
Cetirizine Hydrochloride Zyrtec Dry Syrup 1.25%, Zyrtec tablets 5mg [*1]	UCB Japan Co. Ltd	April 22, 2009
Somatropin (genetical recombination) NORDITROPIN S injection 5mg and 10mg, Norditropin NordiFlex injection 5mg, 10mg and 15mg [*4]	Novo Nordisk Pharma Ltd.	April 22, 2009
Doxorubicin Hydrochloride DOXIL Injection 20mg [*5]	Janssen Pharmaceutical K.K.	April 22, 2009
Sodium Chloride/Potassium Chloride/Sodium Bicarbonate/Anhydrous Sodium Sulfate Niflec for internal use [*6]	Ajinomoto Pharma Co., Ltd.	April 22, 2009
Mosapride Citrate Gasmotin Tablets 2.5 mg and 5 mg, Gasmotin Powder [*7]	Dainippon Sumitomo Pharma Co., Ltd.	April 22, 2009

*1: An additional administration for “pediatrics”

*2: An additional indication for “remission of various symptoms of chronic obstructive pulmonary disease (COPD) (including chronic bronchitis and emphysema) (for patients who require concomitant use of inhaled corticosteroids and long acting inhaled beta-2 stimulant)”

*3: An additional indication for “prophylaxis of venous thromboembolisms in patients undergoing abdominal surgery who are at risk for thromboembolic complications”

*4: An additional indication for “treatment of growth hormone hyposecretion in adult (restricted to serious cases)”

*5: An additional indication for “treatment of ovarian cancer that has progressed after chemotherapy”

*6: An additional indication for “cleansing of the colon as a preparation prior to radiographic contrast barium enema”

*7: An additional indication for “adjunction with colonic cleansing agent for a preparation prior to radiographic contrast barium enema”