# Pharmaceuticals and Medical Devices Safety Information

## No. 243 January 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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| **Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare** | **Pharmaceuticals and Medical Devices Agency** |
| Pharmaceutical and Food Safety Bureau,<br>Ministry of Health, Labour and Welfare<br>1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo<br>100-8916 Japan | Office of Safety,<br>Pharmaceuticals and Medical Devices Agency<br>3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo<br>100-0013 Japan<br>E-mail: safety.info@pmda.go.jp |


*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. 243 January 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. 193)

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 November 30 and December 26, 2007.

## 1 <Antipyretics and analgesics, anti-inflammatory agents>
## Flurbiprofen (oral dosage form)

**[Brand Name]**

Froben granules 8%, Froben tablets 40 (Kaken Pharmaceutical Co., Ltd.) and others

**[Adverse Reactions (clinically significant adverse reactions)]**

**Aplastic anaemia:** Aplastic anaemia has been reported. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

**Toxic epidermal necrolysis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome), dermatitis exfoliative:** Toxic epidermal necrolysis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and dermatitis exfoliative may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

## 2 <Antipyretics and analgesics, anti-inflammatory agents>
## Flurbiprofen Axetil

**[Brand Name]**

Ropion Injection 50 mg (Kaken Pharmaceutical Co., Ltd.)

**[Adverse Reactions (clinically significant adverse reactions)]**

**Toxic epidermal necrolysis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome), dermatitis exfoliative:** Toxic epidermal necrolysis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and dermatitis exfoliative may occur. Patients should be carefully observed, and if such abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

## 3 <Skeletal muscle relaxants>
## Botulinum Toxin Type A

**[Brand Name]**

Botox Injection 100 (GlaxoSmithKline K.K.)

**[Precautions of Dosage and Administration]**

<Blepharospasm>
Blepharoptosis may occur. Injection near the levator palpebrae superioris should be avoided.
<Spasmodic torticollis>
Caution should be exercised when administering into the levator scapulae, since the injection may be associated with an increased risk of dysphagia and respiratory infection.

**[Important Precautions]**

Injection of botulinum toxin may cause adverse events which are possible related to spread of botulinum toxin distant from the site of administration. Deaths associated with dysphagia, pneumonia and/or significant debility have been reported. Extreme caution should be exercised when administering this drug to patients with neurological disorder such as dysphagia because of an increased risk of these adverse events.

**Since feelings of weakness, muscle weakness, dizziness and visual acuity reduced may occur after administration of this drug, the patient should be cautioned when performing potentially hazardous tasks, such as operating an automobile or machinery**.

**[Adverse Reactions (clinically significant adverse reactions)]**

**Shock, anaphylactoid reactions, serum sickness:** Shock, anaphylactoid reactions and serum sickness may occur. This drug should therefore be administered with precautionary methods against these symptoms.
After administration of this drug, the patient's clinical condition should be closely monitored for any changes, such as nausea, to check that no abnormalities have occurred. If symptoms, such as dyspnea, generalized flushing, angioedema and rash, etc. occur, this drug should be discontinued immediately, and appropriate measures, such as maintaining blood pressure, fluid replacement/management, and maintaining the airway, should be taken.

**Convulsive seizures**: New onset or recurrent convulsive seizures have been reported. If such symptoms are observed, appropriate measures should be taken. Caution should be administered particularly when patients have a history of convulsive seizures.

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## 4 <Miscellaneous> Everolimus

**[Brand Name]**

Certican Tablets 0.25 mg, 0.5 mg, and 0.75 mg (Novartis Pharma K.K.)

**[Adverse Reactions (clinically significant adverse reactions)]**

**Pulmonary alveolar proteinosis:** Pulmonary alveolar proteinosis may occur. Patients should be carefully monitored. If abnormalities are observed, appropriate measures, such as discontinuation of the drug should be taken.

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## 5 <Synthetic antibacterials> Garenoxacin Mesilate Hydrate

**[Brand Name]**

Geninax Tablets 200 mg (Toyama Chemical Co., Ltd.)

**[Important Precautions]**

Shock, anaphylactoid reactions have been reported. Complete medical histories including histories of allergies and drug hypersensitivity should be taken before initiating therapy with this drug.

**[Adverse Reactions (clinically significant adverse reactions)]**

**Shock, anaphylactoid reactions (dyspnoea, oedema, redness, etc.):** Shock, anaphylactoid reactions may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

**<Reasons for revisions of 6 and 7 below>**

The MHLW has provided information regarding possible occurrence of abnormal behaviour in pediatric and adolescent influenza patients to healthcare providers through various related organisations by issuing "To All Healthcare Providers Involved in Influenza Treatment (Request for Precautions After Initiating Influenza Treatment)" (February 28, 2007). As results of the investigations by the Subcommittee of the Committee on Drug Safety, under the Pharmaceutical Affairs and Food Sanitation Council regarding "oseltamivir phosphate (Tamiflu)" (December 25, 2007), the MHLW has requested the marketing authorisation holder to revise the PRECAUTION section in order to remind the healthcare providers of the abnormal behaviour.

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## 6 < Antiparkinsonian agents> Amantadine Hydrochloride

**[Brand Name]**

Symmetrel Fine Granules 10%, Symmetrel Tablets 50 mg and 100 mg (Novartis Pharma K.K.) and others

**[Important Precautions]**

Use of this drug for "Influenza A virus infection"

It has been reported that psychoneurotic symptoms including abnormal behaviour occurred after administration of this drug, although the causal relationship to this drug is unknown. When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, ①abnormal behaviour may occur and ②caregivers should be careful not to let patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents including falls due to abnormal behaviour. Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

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## 7 < Antivirals> Zanamivir Hydrate

**[Brand Name]**

Relenza (GlaxoSmithKline K.K.)

**[Important Precautions]**

It has been reported that psychoneurotic symptoms including abnormal behaviour occurred after administration of this drug, although the causal relationship to this drug is unknown. When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, ①abnormal behaviour may occur and ②caregivers should be careful not to let patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents including falls due to abnormal behaviour. Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

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# 2

# List of products subject to Early Post-marketing Phase Vigilance

(As of January 1, 2008)

| Nonproprietary name<br>Brand name | Name of the marketing authorisation holder | Date of EPPV initiation |
|---|---|---|
| Carteolol Hydrochloride<br>Mikelan LA Ophthalmic Solution 1% and 2% | Otsuka Pharmaceutical Co., Ltd. | July 3, 2007 |
| Darbepoetin Alfa (Genetical recombination)<br>Nesp Injection Syringe 10 µg syringe, 15 µg syringe, 20 µg syringe, 30 µg syringe, 40 µg syringe, 60 µg syringe, and 120 µg syringe | Kirin Pharma Company, Limited | July 9, 2007 |
| Fludarabine Phosphate<br>Fludara Tab. 10 mg | Bayer Yakuhin, Ltd. | July 12, 2007 |
| Estradiol<br>l'estrogel 0.06% | Shiseido Co., Ltd. | August 9, 2007 |
| Tadalafil<br>Cialis Tablets 5 mg, 10 mg, and 20 mg | Eli Lilly Japan K.K. | September 12, 2007 |
| Topiramate<br>Topina Tablets 50 mg and 100 mg | Kyowa Hakko Kogyo Co., Ltd. | September 26, 2007 |
| Montelukast Sodium<br>Kipres Fine Granules 4 mg | Kyorin Pharmaceutical Co., Ltd. | October 2, 2007 |
| Montelukast Sodium<br>Singulair Fine Granules 4 mg | Banyu Pharmaceutical Co., Ltd. | October 2, 2007 |
| Rocuronium Bromide<br>Eslax Intravenous 25 mg/2.5 mL and 50 mg/5.0 mL | Nippon Organon K.K. | October 2, 2007 |
| Garenoxacin Mesilate Hydrate<br>Geninax Tablets 200 mg | Toyama Chemical Co., Ltd. | October 5, 2007 |
| Idursulfase (Genetical recombination)<br>Elaprase Solution for Intravenous Drip 6 mg | Genzyme Japan K.K. | October 17, 2007 |
| Pilocarpine Hydrochloride<br>Salagen Tablets 5 mg[*1] | Kissei Pharmaceutical Co., Ltd. | October 19, 2007 |
| Nicorandil<br>Sigmart Injection 2 mg, 12 mg, and 48 mg[*2] | Chugai Pharmaceutical Co., Ltd. | October 19, 2007 |
| Clopidogrel Sulfate<br>Plavix Tablets 25 mg and 75 mg[*3] | Sanofi-Aventis K.K. | October 19, 2007 |
| Loratadine<br>Claritin Tablets 10 mg, Claritin RediTab Tablets 10 mg[*4] | Schering-Plough K.K. | October 19, 2007 |
| Travoprost<br>Travatanz Ophthalmic Solution 0.004% | Alcon Japan Ltd. | October 25, 2007 |
| Strontium Chloride ($^{89}$Sr)<br>Metastron Injectable | Nihon Medi-Physics Co., Ltd. | October 31, 2007 |
| Eplerenone<br>Selara Tablets 25 mg, 50 mg, and 100 mg | Pfizer Japan Inc. | November 13, 2007 |

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|---|---|---|
| Estradiol<br>Divigel 1 mg | Pola Pharma Inc. | November 20, 2007 |
| Imiquimod<br>Beselna Cream 5% | Mochida Pharmaceutical Co., Ltd. | December 10, 2007 |
| Darunavir Ethanolate<br>Prezista Tablets 300 mg | Janssen Pharmaceutical K.K. | December 10, 2007 |
| Insulin Detemir (Genetical recombination)<br>Levemir 300, Levemir 300 FlexPen | Novo Nordisk Pharma Ltd. | December 14, 2007 |
| Nelarabine<br>Arranon G Injection 250 mg | GlaxoSmithKline K.K. | December 14, 2007 |
| Erlotinib Hydrochloride<br>Tarceva Tablets 25 mg, 100 mg, and 150 mg | Chugai Pharmaceutical Co., Ltd. | December 18, 2007 |
| Methylphenidate Hydrochloride<br>Concerta Tablets 18 mg and 27 mg | Janssen Pharmaceutical K.K. | December 19, 2007 |
| Beraprost Sodium<br>Careload LA Tablets 60 μg | Toray Industries, Inc. | December 19, 2007 |
| Beraprost Sodium<br>Berasus LA Tablets 60 μg | Kaken Pharmaceutical Co., Ltd. | December 19, 2007 |

*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”

Reference Material

# Information on oseltamivir phosphate (Tamiflu)

## <The brief summary of the results of the investigation by the Subcommittee on Drug Safety (held on December 25, 2007)>

The brief summary of the results of the investigation on “oseltamivir phosphate (Tamiflu)” by the Subcommittee of the Committee on Drug Safety under the Pharmaceutical Affairs and Food Sanitation Council (held on December 25, 2007) 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.

**December 25, 2007**

**Subcommittee on Drug Safety**
**Committee on Drug Safety**
**Pharmaceutical Affairs and**
**Food Sanitation Council**

**Oseltamivir Phosphate (Tamiflu)**

**This subcommittee held meetings to decide on a conclusion with regard to a relationship between the administration of oseltamivir phosphate (Tamiflu) and adverse reactions such as abnormal behaviour on April 4, June 16, and November 11, 2007. A hearing was conducted on June 16, 2007 to obtain statements of opinion from organizations collecting information on the safety of Tamiflu. In addition, investigations have been continuing on the reports on the status of reviews provided by the Oseltamivir Phosphate Non-clinical Working Group (Non-clinical WG) and Oseltamivir Phosphate Clinical Working Group (Clinical WG) on June 16 and November 11, 2007** (Note 1).

(Note 1) Refer to the reference materials for the progress on the safety measures for Tamiflu.

**Today, this subcommittee conducted an investigation of the review results reported by the Non-clinical WG and Clinical WG, as shown in Appendix 1 and 2, respectively. The results of the present review by this subcommittee regarding the relationship between Tamiflu intake and abnormal behaviour or sudden death are as follows.**

<Editing note: The underlined materials are not referable.>

○ **Today, this subcommittee received reports on results of non-clinical studies (animal experiments, etc.), clinical studies, and epidemiological surveys (currently, have not reached the analysis stage necessary to obtain a clear conclusion) from the Non-clinical WG and Clinical WG. Although at present there have not been any results obtained that suggest a causal relationship between Tamiflu intake and abnormal behaviour or sudden death, it is appropriate to continue to make progress with thorough and careful investigation and analysis of epidemiological surveys and clinical studies in particular, which should be reported to the Clinical WG and this subcommittee as soon as possible.**

(1) Non-clinical Studies
Results of binding assays showed that the brain concentrations of Tamiflu and active metabolite that are estimated when the clinical dose is administered are not thought to have multiple effects on CNS (central nerves system) receptors and ion channels. And others.

(2) Clinical Studies
Based on an interim analysis of the sleep laboratory study, it was confirmed that Tamiflu did not cause dyssomnia, and there were no clear changes noted in ECG tests. And others.

○ **Based on these results, this subcommittee will progress with further review of results from non-clinical studies, clinical studies and epidemiological surveys, etc., that are currently being conducted or analysed in the Non-clinical WG and Clinical WG, and will decide on a final conclusion as soon as possible.**

○ **It is necessary to remind healthcare providers and the public of abnormal behaviour that may occur due to influenza.**

○ **Based on the above, the measures being taken for Tamiflu** (Note 2) **are still valid at the present time, and healthcare providers, patients and their families, etc. should be kept alerted.**

(Note 2) Dear Healthcare Professional Letter issued on March 20, 2007:

Abnormal behaviour that have resulted in accidents such as falls have been reported in patients aged 10 to 19 years following administration of this drug, although the causal relationship to this drug is unknown. As a general rule, this drug should not be used in these patients for the above reason except that the patient is considered a high-risk patient based on complications and past history, etc. When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, ①abnormal behaviour may occur and ②caregivers should be careful not to let patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents.
Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

○ **Furthermore, with regard to zanamivir hydrate (Relenza) and amantadine hydrochlorate (Symmetrel, etc.), the following points should be added to the PRECAUTIONS in the package insert, and efforts should be made to remind healthcare professionals, patients and their caregivers, etc. of the possibility of abnormal behaviour occurring in children and adolescents with influenza.**

- **It has been reported that psychoneurotic symptoms including abnormal behaviour occurred after administration of this drug, although the causal relationship to this drug is unknown. When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, ①abnormal behaviour may occur and ②caregivers should be careful not to let patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents including falls due to abnormal behaviour. Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.**