# Pharmaceuticals and Medical Devices Safety Information

## No. 238 July 2007

### 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).


**Published by**

**Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare**

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

**Translated by**

**Pharmaceuticals and Medical Devices Agency**

Office of Safety,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
**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).*

**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

# 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 June 1, 2007.

## 1 Zolpidem Tartrate

| | |
|---|---|
| **Brand Name (name of company)** | Myslee Tablets 5 mg and 10 mg (Astellas Pharma Inc.) |
| **Therapeutic Category** | Hypnotics and sedatives, anxiolytics |
| **Indications** | Insomnia (excluding insomnia associated with schizophrenia or manic-depressive illness) |

**<Reason for Revision>**

It has been described that psychiatric symptoms and transient anterograde amnesia etc. might occur in patients treated with this drug in the "Clinically significant adverse reactions" section of the package insert and that the drug should be taken immediately before bedtime in the "Important precautions" section as well. However, recently in the United States, the product labeling for hypnotic agent has been, as a whole, revised to call for a further alert to hypnotic agent-induced adverse drug reactions such as parasomnia. In view of the content of the revision as well as reported adverse reaction cases in Japan, MHLW has called for reminding healthcare professionals of the above alert by revision of the package insert to include the following description in an additional "WARNING" section, although there has already been a similar description given in the content.

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

**[Warning]**

**WARNING**

A twilight state or parasomnia (such as symptoms of somnambulism, etc.) may occur after taking this product. In addition, patients may not remember events that occur between drug ingestion and sleep onset or after arousal from sleep. Therefore, caution should be exercised.

**[Precautions of Dosage and Administration]**

The response to this product varies among patients, and the onset of twilight state and incidences of parasomnia (such as symptoms of somnambulism, etc.) possibly occur dose-dependently; therefore initiate treatment with a low dose (5 mg in a single dose). If an increased dose is necessary, this product should be administered cautiously with close monitoring of the patient's condition. The total daily dosage should not exceed 10 mg. The dose should be reduced as symptoms improve.

Patients should be instructed to take this product immediately before bedtime. Amnesia has been reported after ingestion of this product at bedtime when a patient did not allow sufficient sleep time until rising for the day's activities or when a patient rose temporarily and worked during sleep time. Therefore, patients should be instructed not to take this product if there is a possibility that daily activities will commence before the effects of the drug wear off.

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

**Psychiatric symptoms, consciousness disturbed**: Since psychiatric symptoms and consciousness disturbed, such as delirium, confusion, symptoms of somnambulism, hallucinations, excitement, disinhibition, and depressed level of consciousness, may occur, patient's condition should be observed carefully. If any abnormal findings occur, administration of this product should be discontinued.

**Transient anterograde amnesia, twilight state**: Transient anterograde amnesia (The patient does not remember events that occur between drug ingestion and sleep onset or after arousal from sleep.) and twilight state may occur. Therefore, the patients should be instructed to go to bed immediately after taking this product and they should not be waken up during sleeping. Cases have been reported in which patients have driven a car, eaten a meal, etc. in a state of incomplete arousal from sleep and did not remember the events. If any abnormal findings occur, administration of this product should be discontinued.

**<Reference Information>**

The number of reported adverse reaction cases in about the last 3 years (April 1, 2004 to May 10, 2007) (events for which a causality to the drug could not be denied)

• Twilight state, parasomnia: 12 cases (no fatal case)

The number of patients treated with zolpidem for a year estimated by MAH (Marketing Authorisation Holder): approximately 2 million (2006)

Marketed in Japan in: December 2000

## Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 60s | Insomnia (hypertension, diabetes mellitus, late effects of cerebral infarction, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) | 10 mg 1 day | **Delirium**<br>4 days before administration:<br>The patient was taking 0.25 mg of brotizolam every night for insomnia (She stopped taking the drug since then).<br>On day 1 of administration:<br>11 pm. The patient took 10 mg of zolpidem tartrate. She had a visitor immediately thereafter. Her husband noticed her abnormal behavior during the visit. The patient made impolite and strange comments, such as "Drink it up" and "I'm falling to the bottom of the valley".<br>On day 2 of administration:<br>0:20 am The patient visited the hospital. She answered with obscure responses, such as "I'm in the mountain". She was hospitalized to follow up.<br>0:45 am. Blood pressure was 186/84 mmHg.<br>0:50 am. The patient received 5 mg of sublingual nifedipine. The patient was aroused (able to respond). She said, "I don't remember much since taking a new hypnotic agent".<br>1:00 am. Blood pressure was 170/70 mmHg. The doctor confirmed the patient was clear in consciousness. Observation was continued for a while.<br>1:45 am. Blood pressure was 142/76 mmHg. The patient was discharged to home. No hepatic function disorder was considered. The patient had no habit of drinking alcohol. No abnormal behaviors occurred with brotizolam as well as triazolam and quazepam, which were administered later. |

| | |
|---|---|
| | Concomitant medications: spironolactone, carvedilol, temocapril hydrochloride, doxazosin mesilate, acarbose, azosemide, amlodipine besilate, stomachics and digestives, ibudilast, ticlopidine hydrochloride, mexiletine hydrochloride, insulin human (genetical recombination). |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Female 60s | Insomnia (hyperlipidaemia, gastritis, hypertension, anxiety neurosis) | 10 mg 139 days | **Delirium**<br>On day 139 of administration:<br>The patient was living alone. She went to bed after taking 10 mg of zolpidem tartrate at night.<br>On day 140 of administration (day of discontinuation):<br>Dumplings that should have been in the refrigerator were all gone when the patient woke up in the morning. She didn't remember if she had eaten them (It was considered that the patient ate them probably as a result of delirium onset).<br>13 days after discontinuation:<br>Since the abnormal behavior was considered to be related to this drug, the medication was switched to another agent. No particular symptoms have been observed since then. |
| | Concomitant medications: cerivastatin sodium, irsogladine maleate, and troxipide | | | |

## 2 Zopiclone

| | |
|---|---|
| **Brand Name (name of company)** | Amoban Tablets 7.5 and 10 (Sanofi-Aventis K.K.)<br>Amobantes 7.5 (Kobayashi Kako Co., Ltd.)<br>Antomylin Tab. 7.5 (Towa Pharmaceutical Co., Ltd.)<br>Slowheim Tablets 7.5 and 10 (Kyowa Pharmaceutical Industry Co., Ltd.)<br>Zopicool Tablets 7.5 and 10 (Sawai Pharmaceutical Co., Ltd.)<br>Zopiban Tablets 7.5 (Choseido Pharamceutical Co., Ltd.)<br>Dopareel Tablets 7.5 and 10 (KYORIN Rimedio Co. Ltd.)<br>Metrom Tablets 7.5 and 10 (Tatsumi Kagaku Co., Ltd.) |
| **Therapeutic Category** | Hypnotics and sedatives, anxiolytics |
| **Indications** | ○Insomnia<br>○Anaesthetic premedication |

**<Reason for Revision>**

It has been described that psychiatric symptoms and transient anterograde amnesia etc. might occur in patients treated with this drug in the "Clinically significant adverse reactions" section of the package insert and that the treatment should be initiated with a low dose and the drug should be taken immediately before bedtime in the "Important precautions" section as well. However, recently in the United States, the product labeling for hypnotic agent has been, as a whole, revised to call for a further alert to hypnotic agent-induced adverse drug reactions such as parasomnia. In view of the content of the revision as well as reported adverse reaction cases in Japan, MHLW has called for reminding healthcare professionals of the above alert by revision of the package insert to include the following description in an additional "WARNING" section, although there has already been a similar description given in the content

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

**[Warning]**

**WARNING**

A twilight state or parasomnia (such as symptoms of somnambulism, etc.) may occur after taking this product. In addition, patients may not remember events that occur between drug ingestion and sleep onset or after arousal from sleep. Therefore, caution should be exercised.

**[Precautions of Dosage and Administration]**

The response to this product varies among patients; therefore initiate treatment with a low dose (3.75 mg in a single dose for elderly patients). For patients with liver disorder, initiating treatment with a dose of 3.75 mg is recommended. If an increased dose is necessary, this product should be administered cautiously with close monitoring of the patient's condition. The total daily dosage should not exceed 10 mg. The dose should be reduced as symptoms improve.

Patients should be instructed to take this product immediately before bedtime for insomnia. Patients should be instructed not to take this product if there are possibilities such as that when a patient rose temporarily and worked during sleep time after ingestion of this product at bedtime.

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

**Psychiatric symptoms, consciousness disturbed:** Since psychiatric symptoms and consciousness disturbed, such as hallucinations, delirium, confusion, symptoms of somnambulism, nightmare, irritability, aggression, and abnormal behaviour, may occur, patient's condition should be observed carefully. If any abnormal findings occur, administration of this product should be discontinued.

**Transient anterograde amnesia, twilight state**: Since transient anterograde amnesia (The patient does not remember events that occur after arousal from sleep.) and twilight state may occur, precautions should be taken when administering this product, such as initiating treatment with a low dose. Cases have been reported in which patients have driven a car, eaten a meal, etc. in a state of incomplete arousal from sleep and did not remember the events. If any abnormal findings occur, administration of this product should be discontinued.

**<Reference Information>**

The number of reported adverse drug reaction cases in about the last 3 years (April 1, 2004 to April 30, 2007) (events for which a causality to the drug could not be denied)

• Twilight state, parasomnia: 4 cases (no fatal case)

The number of patients treated with zopiclone for a year estimated by MAH: approximately 1.1 million (2006)

Marketed in Japan in: June 1989

## Case Summary

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 1 | Female 70s | Psychosomatic disease (diabetes mellitus, hypertension, chronic pancreatitis, gastritis atrophic, hyperlipidaemia, constipation, back pain, and anorexia) | 7.5 mg 1 year and 26 days | **Transient anterograde amnesia**<br>On day 1 of administration:<br>The patient complained insomnia due to emotional stress. Treatment was started with 7.5 mg of zopiclone as needed in the case of insomnia (actual dose taken was 3.75–7.5 mg/dose).<br>On day 132 of administration:<br>The treatment was changed from as needed to a dose of 7.5 mg before bedtime. The patient started taking 7.5 mg of zopiclone every day around that time.<br>The patient experienced reduced food intake due to emotional stress and was encouraged to eat more by her physician.<br>Approx. 5th month of administration:<br>During the treatment, she had experienced nightmare and eating at midnight unconsciously. By the approx. 1 year and 1st month of zopiclone administration, she always developed these symptoms after taking this drug.<br>1 year and 11th day of administration:<br>The patient was able to sleep without taking zopiclone. No nightmare and night-time eating occurred. She drank alcohol twice a week for a few weeks, but no symptoms occurred without the drug.<br>1 year and 26th day of administration (day of discontinuation):<br>Zopiclone was discontinued.<br>1 month after discontinuation:<br>No symptoms occurred after discontinuation of zopiclone. |
| | Concomitant medications: amlodipine besilate, pravastatin sodium, sennoside, octotiamine/$B_2$/$B_6$/$B_{12}$, teprenone, tizanidine hydrochloride | | | |

| No. | Patient | | Daily dose/ Treatment duration | Adverse reactions |
|---|---|---|---|---|
| | Sex/Age | Reason for use (complications) | | Clinical course and therapeutic measures |
| 2 | Male 80s | Insomnia (rheumatoid arthritis, herpes zoster, hypotension, constipation, and urinary incontinence) | 7.5 mg 1 day | **Incontinence, symptoms of somnambulism, and memory deficit**<br>On day 1 of administration:<br>After taking 7.5 mg of zopiclone for insomnia, the patient has no memories of the following events due to twilight state.<br>3 hours after administration:<br>He took off his wet underwear.<br>6 hours after administration:<br>He walked to the bathroom.<br>9 hours after administration:<br>He was wandering around during the night. He had incontinence but had a vague memory of it. |
| | Concomitant medications: sulindac, goshajinkigan, cobamamide, nucleoside/suprifen hydrochloride, dihydroergotamine mesilate, pantethine, magnesium oxide, oxybutynin hydrochloride, sennoside, aciclovir | | | |

# 2

# Revision of PRECAUTIONS (No. 188)

## 1. Drugs

This section presents details of revisions of "PRECAUTIONS" in package inserts and brand names of drugs that have been revised according to the Notification dated June 1, 2007 (excluding those presented in "1. Important Safety Information" of this Bulletin).

---

### 1 <Hypnotics and sedatives, anxiolytics> Triazolam

**[Brand Name]**

Halcion Tablets 0.125 mg and 0.25 mg (Pfizer Japan Inc.) and others

**[Warning]**

**WARNING**

A twilight state or parasomnia (such as symptoms of somnambulism, etc.) may occur after taking this product. In addition, patients may not remember events that occur between drug ingestion and sleep onset or after arousal from sleep. Therefore, caution should be exercised.

**[Precautions of Dosage and Administration]**

The response to this product varies among patients, and adverse reactions such as sleepiness, dizziness, light-headed feeling, and amnesia possibly occur dose-dependently; therefore initiate treatment with a low dose (0.125mg or less in a single dose). If an increased dose is necessary, this product should be administered cautiously with close monitoring of the patient's condition. The total daily dosage should not exceed 0.5 mg. The dose should be reduced as symptoms improve.

Patients should be instructed to take this product immediately before bedtime for insomnia. Amnesia has been reported after ingestion of this product at bedtime when a patient did not allow sufficient sleep time until rising for the day's activities or when a patient rose temporarily and worked during sleep time. Therefore, patients should be instructed not to take this product if there is a possibility that daily activities will commence before the effects of the drug wear off.

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

**Psychiatric symptoms**: Since psychiatric symptoms such as irritable excitement, confusion, aggression, symptoms of somnambulism, hallucinations, delusion, and agitation may occur, patient's condition should be observed carefully. If any abnormal findings occur, administration of this product should be discontinued. Extreme caution should be exercised when administering this drug to patients with mental disorders such as schizophrenia.

**Transient anterograde amnesia, twilight state**: Transient anterograde amnesia (The patient does not remember events that occur after arousal from sleep.) and twilight state may occur. Therefore, this product should be administered with caution, such as initiating treatment with a low dose. Cases have been reported in which patients have driven a car, eaten a meal, etc. in a state of incomplete arousal from sleep and did not remember the events. If any abnormal findings occur, administration of this product should be discontinued.

**<Reason for Revision>** It has been described that psychiatric symptoms and transient anterograde amnesia might occur in patient treated with this drug in the "WARNING" and the "Clinically significant adverse reactions" sections of the package insert and that the treatment should be initiated with a low dose and the drug should be taken immediately before bedtime in the "Important precautions" section as well. However, recently in the United States, the product labeling for hypnotic agent has been, as a whole, revised to call for a further alert to hypnotic agent-induced adverse drug reactions such as parasomnia. In view of the content of the revision as well as reported adverse reaction cases in Japan, MHLW has called for reminding healthcare professionals of the above alert by revision of the package insert to include the following description in a "WARNING" section, although there has already been a similar description given in the content.

---

## 2 <Miscellaneous metabolism agents> Mycophenolate Mofetil

**[Brand Name]** CellCept Capsules 250 (Chugai Pharmaceutical Co., Ltd.)

**[Adverse Reactions (clinically significant adverse reactions)]** **Severe diarrhoea**: Severe diarrhoea may occur and cases of dehydration also have been reported; therefore patients should be carefully observed. If any abnormal findings occur, appropriate measures such as administration of antidiarrhoeics or fluid replacement should be taken depending on the patients' conditions. In addition, dose reduction or drug withdrawal should be considered as needed.

---

## 3 <Antineoplastics-Miscellaneous> Carboplatin

**[Brand Name]** Paraplatin Injection 50 mg, 150 mg, and 450 mg, Paraplatin for Injection 150 mg (Bristol-Myers K.K.) and others

**[Adverse Reactions (clinically significant adverse reactions)]** **Deafness**:Deafness and tinnitus etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as drug discontinuation should be taken.

## 2. Medical Devices

This section presents details of the revisions of "PRECAUTIONS" in the package inserts of medical devices in accordance with the Notification dated June 15, 2007.

---

### 1 Enteral feeding tubes and gastric tubes (only those with stylet or guide wire as kits)

**[Warning]**

**WARNING**

Stylet or guide wire (hereinafter referred to as "stylet, etc.") should be handled with caution. [Improper use of stylet, etc. will increase the risk of injury to organs in patients and breaks of tube.]

**[Contraindications]**

1) Do not remove stylet, etc. until correct placement of tube is confirmed. Never reinsert stylet, etc. [The tip of reinserted stylet, etc. may pass through a side hole of the tube and injure wall of the digestive tracts such as stomach and intestine.]
2) Do not use stylet, etc. for clearing tube obstruction or any other purposes other than original intended use (tube placement support).

**[Precautions]**

1) Caution should be exercised against injury to tracheal wall and improper insertion and placement of tubes in the trachea/lungs. If pressure resistance is experienced or coughs are induced while inserting a tube, subsequent insertion should be avoided, and the tube should be removed before reinsertion, since there is a possibility of improper insertion into the lung. [Injury to the lungs or introduction of fluids such as nutrition supplements may cause pulmonary function impairment.]
2) During insertion and placement of a tube, correct position of the tube tip should be confirmed using several methods such as x-ray, aspiration of gastric juice, listening to bubbling sound, or checking the position of tube marking.
3) Stylet, etc. should be handled with caution. If stylet, etc. itself cannot be removed because of resistance, etc. remove it along with the tube. [Forceful removal of stylet, etc. may cause breaks in the tube.]
4) The removed tube should not be reused.

**[Important Precautions]**

1) Flushing of a tube should be performed using lukewarm water before and after administration of nutrition. [Obstruction of tube due to the accumulation of residuals such as nutrition supplements should be prevented.]
2) Caution should be exercised when administering powder etc. (especially drugs containing additives such as binder) through tube because it may lead to tube obstruction.
3) Procedures should be stopped when pressure resistance is experienced during administration such as of nutrition supplements or during flushing of tube using lukewarm water etc. [There is a possibility of tube lumen obstruction. If procedures are continued without clearing obstruction of the tube lumen, inner tube pressure will excessively increase and breaks or cracks of the tube may occur.]
4) The following precautions should be observed in clearing obstruction of a tube. However, a tube with higher risk of breaks or cracks (e.g., a tube with small diameter and thin wall thickness used for newborns/infants/children) is obstructed, those procedures should not be performed, and the tube should be removed.
   ① Large syringes should be used (based on manufactures' data, "○ mL and more is recommended" should be described.). [Using syringes ○ mL or less is associated with the increased injection pressure and the risk of breaks or cracks of a tube.]
   ② A stylet, etc. should not be used.
   ③ If obstruction of tube is not cleared by those procedures, the tube should be removed.

## 2 Enteral feeding tubes and gastric tubes (excluding those applicable to 1)

**[Contraindications]**

Do not use insertion/placement methods that are not indicated in the package insert of this product, such as use of stylet or guide wire (hereinafter referred to as "stylet, etc."). [Since stylet, etc. is elastic and has small outer diameter, there is a higher risk of improper insertion into trachea. In addition, the tip of inserted stylet, etc. may pass through a side hole of the tube and injure wall of digestive tracts such as stomach and intestine.]

**[Precautions]**

1) Caution should be exercised against injury to tracheal wall and improper insertion and placement of tubes in the trachea/lungs. If pressure resistance is experienced or coughs are induced while inserting a tube, subsequent insertion should be avoided, and the tube should be removed before reinsertion, since there is a possibility of improper insertion into the lung. [Injury to the lungs or introduction of fluids such as nutrition supplements may cause pulmonary function impairment.]
2) During insertion and placement of a tube, correct position of the tube tip should be confirmed using several methods such as x-ray, aspiration of gastric juice, listening to bubbling sound, or checking the position of tube marking.
3) The removed tube should not be reused.

**[Important Precautions]**

1) Flushing of a tube should be performed using lukewarm water before and after administration of nutrition. [Obstruction of tube due to the accumulation of residuals such as nutrition supplements should be prevented.]
2) Caution should be exercised when administering powder etc. (especially drugs containing additives such as binder) through tube because it may lead to tube obstruction.
3) Procedures should be stopped when pressure resistance is experienced during administration such as of nutrition supplements or during flushing of tube using lukewarm water etc. [There is a possibility of tube lumen obstruction. If procedures are continued without clearing obstruction of the tube lumen, inner tube pressure will excessively increase and breaks or cracks of the tube may occur.]
4) The following precautions should be observed in clearing obstruction of a tube. However, a tube with higher risk of breaks or cracks (e.g., a tube with small diameter and thin wall thickness used for newborns/infants/children) is obstructed, those procedures should not be performed, and the tube should be removed.
   ① Large syringes should be used (based on manufactures' data, "○ mL and more is recommended" should be described. ). [Using syringes ○ mL or less is associated with the increased injection pressure and the risk of breaks or cracks of a tube.]
   ② A stylet, etc. should not be used.
   ③ If obstruction of tube is not cleared by those procedures, the tube should be removed.

## 3 Gastric fistula (intestinal fistula) tubes

**[Important Precautions]**

1) Flushing of a tube should be performed using lukewarm water before and after administration of nutrition. [Obstruction of tube due to the accumulation of residuals such as nutrition supplements should be prevented.]
2) Caution should be exercised when administering powder etc. (especially drugs containing additives such as binder) through tube because it may lead to tube obstruction.
3) Procedures should be stopped when pressure resistance is experienced during administration such as of nutrition supplements or during flushing of tube using lukewarm water etc. [There is a possibility of tube lumen obstruction. If procedures are continued without clearing obstruction of the tube lumen, inner tube pressure will excessively increase and breaks or cracks of the tube may occur.]
4) The following precautions should be observed in clearing obstruction of a tube. However, a tube with higher risk of breaks or cracks (e.g., a tube with small diameter and thin wall thickness used for newborns/infants/children) is obstructed, those procedures should not be performed, and the tube should be removed.
   ① Large syringes should be used (based on manufactures' data, "○ mL and more is recommended" should be described.). [Using syringes ○ mL or less is associated with the increased injection pressure and the risk of breaks or cracks of a tube.]
   ② A stylet, etc. should not be used.
   ③ If obstruction of tube is not cleared by those procedures, the tube should be removed.

# 3

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

(As of July 1, 2007)

| Nonproprietary name / Brand name | Name of the marketing authorisation holder | Date of EPPV initiation |
|---|---|---|
| Fexofenadine Hydrochloride / Allegra Tablets 30 mg | Sanofi-Aventis K.K. | November 26, 2007 |
| Perflubutane / Sonazoid for Injection | Daiichi-Sankyo Co., Ltd | January 10, 2007 |
| Pemetrexed Sodium Hydrate / Alimta Injection 500 mg | Eli Lilly Japan K.K. | January 22,2007 |
| Remifentanil Hydrochloride / Ultiva Intravenous 2 mg, and 5 mg | Janssen Pharmaceutical K.K. | January 22,2007 |
| Infliximab (Genetical recombination) / Remicade for I.V. Infusion 100[*1] | Tanabe Seiyaku Co., Ltd. | January 26,2007 |
| Zanamivir Hydrate / Relenza[*2] | GlaxoSmithKline K.K. | January 26,2007 |
| Tacrolimus Hydrate / Prograf Capsules 0.5 mg and 1 mg [*3] | Astellas Pharma Inc. | January 26,2007 |
| Baclofen / Intrathecal Gabalon 0.005%, 0.05%, and 0.2%[*4] | Daiichi-Sankyo Co., Ltd. | January 26,2007 |
| Micafungin Sodium / Funguard 25 mg, 50 mg, and 75 mg for Infusion[*5] | Astellas Pharma Inc. | January 26,2007 |
| Rurioctocog Alfa (Genetical recombination) / Advate Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method 250, 500, and 1000 | Baxter Limited | February 22, 2007 |
| Follitropin Beta (Genetical recombination) / Follistim Inj. 50 and 75[*6] | Nippon Organon K.K. | March 16, 2007 |
| Peginterferon Alfa-2a (Genetical recombination) / Pegasys s.c. 90 μg and 180 μg[*7] | Chugai Pharmaceutical Co., Ltd. | March 16, 2007 |
| Ribavirin / Copegus Tablets 200 mg | Chugai Pharmaceutical Co., Ltd. | March 16, 2007 |
| Modafinil / Modiodal Tablets 100 mg | Alfresa Pharma Corporation | March 28, 2007 |

| | | |
|---|---|---|
| Levonorgestrel-releasing Intrauterine Contraceptive System<br>Mirena 52 mg | Bayer Yakuhin, Ltd. | April 16, 2007 |
| Valaciclovir Hydrochloride<br>Valtrex Granules 50%*8 | GlaxoSmithKline K.K. | April 18, 2007 |
| Entacapone<br>Comtan Tablets 100 mg | Novartis Pharma K.K. | April 19, 2007 |
| Pegvisomant (Genetical recombination)<br>Somavert for s. c. Injection 10 mg, 15 mg, and 20 mg | Pfizer Japan Inc. | June 5, 2007 |
| Salmeterol Xinafoate/Fluticasone Propionate<br>Adoair 100 Diskus, 250 Diskus, and 500 Diskus | GlaxoSmithKline K.K. | June 8, 2007 |
| Ciclesonide<br>Alvesco 50 µg Inhaler 112 puffs, 100 µg Inhaler 112 puffs, and 200 µg Inhaler 56 puffs | Teijin Pharma Limited | June 8, 2007 |
| Fondaparinux Sodium<br>Arixtra Injection 1.5 mg and 2.5 mg | GlaxoSmithKline K.K. | June 8, 2007 |
| Imidafenacin<br>Uritos Tablets 0.1 mg | Kyorin Pharmaceutical Co., Ltd. | June 11, 2007 |
| Imidafenacin<br>Staybla Tablets 0.1 mg | Ono Pharmaceutical Co., Ltd. | June 11, 2007 |
| Ezetimibe<br>Zetia Tablets 10 mg | Schering-Plough K.K. | June 11, 2007 |
| Bevacizumab (Genetical recombination)<br>Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL | Chugai Pharmaceutical Co., Ltd. | June 11, 2007 |
| Celecoxib<br>Celecox Tablets 100 mg and 200 mg | Astellas Pharma Inc. | June 12, 2007 |
| Monobasic Sodium Phosphate Monohydrate/Dibasic Sodium Phosphate Anhydrous<br>Visiclear Tablets | Zeria Pharmaceutical Co., Ltd. | June 15, 2007 |
| Amiodarone Hydrochloride<br>Ancaron Injection 150 | Sanofi-Aventis K.K. | June 22, 2007 |

*1: Additional indication for "the treatment of refractory uveitis in patients with Behcet's disease (only in cases which are not adequately responsive to conventional therapies)"
*2: Additional indication for "the prevention of influenza A or B virus infection"
*3: Additional indication for "Lupus nephritis (when the effect of the administration of steroids is insufficient or administration is difficult due to its adverse reactions)"
*4: Additional administration for "pediatrics"
*5: Additional indication for "the prevention of Aspergillosis and Candidiasis in hematopoietic stem cell transplant patients"
*6: Additional indication for "the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders"
*7: Additional indication for "improvement of viraemia in concomitant use of ribavirin in chronic hepatitis C (1) or (2): (1) serogroup 1 (patients for genotype I (1a) or II (1b) with high blood HCV-RNA load, or (2) patients who failed interferon monotherapy or who developed reactivation of the disease following interferon monotherapy"
*8: Additional indication for "varicella"