Pharmaceuticals and Medical Devices Safety Information

No. 222 February 2006

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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. 222 February 2006

Pharmaceutical and Medical 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

1

Drug Guide for Patients

1. Introduction

Drug Guide for Patients has been posted on the website of Pharmaceuticals and Medical Devices Agency (http://www.info.pmda.go.jp/) since January 31, 2006. In this section, back ground,content, and future time-line is presented.

2. Background

The role of providing information of ethical drugs was discussed in "Council for the Pharmaceutical Information Service Scheme" in 2001. Basic concepts with regard to changes and challenges in circumstances surrounding ethical drugs have been suggested at the council, such as "sufficient information with regard to medical conditions and constitutional predisposition etc. of each patient should be provided" and "quality of the information such as understandability of the content should be sufficiently taken into consideration." As its specific countermeasures, the following items are suggested:

① Enhancement of information provision for patients
- Specific contents and methodology in the instructions for patients should be expeditiously discussed and appropriate measures should be taken.
- Utilization of IT in the future can be considered for medication history management such as a "Medicine notebook" which allows communication with patients.
- Standardization of terminology for subjective symptoms/adverse reactions etc. which can be easily comprehended by patients is necessary to contribute to early detection of serious adverse reactions.

② Enrichment of pharmaceutical information for public
- Regarding information service for the public, information should be provided using that of healthcare providers, arranged in comprehensive format with the involvement of the government.

(September 27, 2001 extract from the final report)

In response, domestic and international investigations regarding specific contents of pharmaceutical information for patients such as "collection of information on medication teaching for physicians/dentists/pharmacists" and "Kusuri-no-Shiori" has been conducted since FY2001. As a result, a proposal regarding the scheme of "Patient medication instruction" has been summarized in April 2005.

Based on the results, the PFSB/SD Notification No. 0630001 of Secretary-General of Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare (MHLW), dated June 30, 2005, "Information regarding 'manual for establishing Drug Guide for Patients'", (hereinafter called "the PFSB/SD Notification ") was issued to present the manual. Furthermore, PFSB/SD Notification No. 1122001・PFSB/CND Notification No. 1122004 of Directors of Safety Division・Compliance and Narcotics Division (CND) of PFSB, MHLW, dated November 22, 2005, "Operation of the Drug Guide for Patients" was issued to present further time-lines etc.

3. Drug Guide for Patients

(1) Objectives

"Drug Guide for Patients" is broadly provided for the public to contribute to the proper understanding of ethical drugs in patients and early detection of serious adverse reactions etc.

(2) Development Method

While Drug Guide for Patients is to be established for the pharmaceuticals with marketing approval by its MAHs (marketing authorization holders), MHLW confirms the congruity of its content with the PFSB/SD Notification, "Manual for Creating Drug Guide for Patients," in advance.

(3) Target Ethical Drugs

It is desirable to establish the "Drug Guide for Patients" especially for the following ethical drugs which require promotion of awareness in patients to contribute to early detection of serious adverse reactions.

- Products with "WARNING" sections in the package insert
- Products with description of "patients should be instructed" to prevent serious adverse reactions etc. under sections "Precautions of Indications", "Precautions of Dosage and Administration", or "Important Precautions" in the package insert.
- Products of which information service regarding proper use is specifically provided to patients

Note that ethical drugs with the warning section are exempt if the descriptions are limited to the following.

- Pay adequate attention to the selection of patients and dosage/administration when administering.
- Prior to using this product, thoroughly read the package insert.
- As serious adverse reactions may occur, this product should be used under supervision of a physician sufficiently experienced in the therapy using this product at an institution capable of carrying out sufficient countermeasures in emergency cases.

(4) Listed Items and Order

Drug Guide for Patients should include items patients should particularly acknowledge prior to using the ethical drug based on the package insert arranged in a way easily understandable. The listed items and order are as follows:

① Establishment date or date of revision
② Brand name
③ Introduction to Drug Guide for Patients
④ Effects of this medicine
⑤ Things that need to be checked before using this medicine
⑥ Proper use of this medicine
⑦ Precautions while using this medicine
⑧ Dosage form
⑨ Component of this medicine
⑩ Others
⑪ Contact information regarding this medicine

(5) Editorial time-lines

	Specified pharmaceuticals subject to establishment of guidelines (prospect)	Date of completion of the draft (prospect)	Date of publication (prospect)
Antidiabetic agents (excluding injectable dosage form)	November 28, 2005[Note 1)]	December 23, 2005	January 31, 2006
Antirheumatic (excluding injectable dosage form) Anticoagulants and antiplatelet agent (excluding injectable dosage form) Anti-asthma drugs (excluding injectable dosage form)	December 16, 2005[Note 2)]	February 13, 2006	March 2006
Standard Commodity Classification for Japan 100s and 200s (excluding injectable dosage form)	until February 2006	until May 2006	July 2006
Standard Commodity Classification for Japan 300s and 400s (excluding injectable dosage form)	until May 2006	until August 2006	October 2006
Standard Commodity Classification for Japan 500s, 600s, 700s, and 800s (excluding injectable dosage form)	until August 2006	until November 2006	January 2007
Injectable dosage form	until November 2006	until January 2007	March 2007

Note 1) An office communication of the Safety Division of PFSB ,MHLW,dated November 28, 2005.

○ List of pharmaceuticals establishment of Drug Guide for Patients is desirable (antidiabetic agents excluding injectable dosage form)

1. Acetohexamide
2. Gliclazide
3. Glyclopyramide
4. Glybuzole
5. Glibenclamide
6. Glimepiride
7. Chlorpropamide
8. Tolbutamide
9. Buformin Hydrochloride
10. Metformin Hydrochloride

Note 2) An office communication of the Safety Division of PFSB ,MHLW, dated December 16, 2005.

○ List of pharmaceuticals establishment of Drug Guide for Patients is desirable (antirheumatic drugs excluding injectable dosage form, anticoagulants and antiplatelet agent excluding injectable dosage form, and anti-asthma drugs excluding injectable dosage form)

1. Methotrexate
2. Leflunomide
3. Warfarin Potassium
4. Cilostazol
5. Ticlopidine Hydrochloride
6. *dl*-Isoproterenol Hydrochloride (inhalant liquid)
7. Orciprenaline Sulfate (inhalant liquid)
8. Salbutamol Sulfate (aerosol and inhalant liquid)
9. Salmeterol Xinafoate
10. Stmerin D
11. Trimetoquinol Hydrochloride (inhalant liquid)
12. Fenoterol Hydrobromide (aerosol)
13. Procaterol Hydrochloride (aerosol, dry powder, and inhalant liquid)

4. Closing comments

Drug Guide for Patients and its content are anticipated to be used via the Internet directly by the public, patients, and their family members. Additionally, the information is available via the Internet directly for the healthcare providers such as physicians, dentists, and pharmacists to use for patient medication instruction.

It is hoped that Drug Guide for Patients will be broadly used to enable early detection of clinically significant adverse reactions by helping patients identify their subjective symptoms from the perspective of further promotion of safety measures for the pharmaceuticals.

2

Revision of PRECAUTIONS

(No. 173)

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 after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 221), together with reference materials.

1 <Psychotropics> Amoxapine

[Brand Name] Amoxan Fine Granules 10%, Amoxan Capsules 10 mg, 25 mg, and 50 mg (Wyeth K.K.)

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Due to a dramatic decrease in dosage or discontinuation of administration, withdrawal symptoms such as emotional instability, chills, confusion, headache, sleep disorder, malaise, queasy, and sweaty etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

2 <Psychotropics> Amitriptyline Hydrochloride

[Brand Name] Tryptanol Tablets-10 and 25 (Banyu Pharmaceutical Co., Ltd.) and others

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.

<Reference Information> Company report

3 <Psychotropics> Imipramine Hydrochloride, Clomipramine Hydrochloride (oral dosage form)

[Brand Name] Imidol Sugar-coated Tablets (10) and (25) (Mitsubishi Pharma Corporation),
Tofranil Tablets 10 mg and 25 mg (Novartis Pharma K.K.)
Anafranil Tablets 10 mg and 25 mg (Alfresa Pharma Corporation)

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Due to a dramatic decrease in dosage or discontinuation of administration, withdrawal symptoms such as queasy, headache, malaise, irritability, emotional instability, sleep disorder, and muscle twitching etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

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4 <Psychotropics> Clomipramine Hydrochloride (injectable dosage form)

[Brand Name] Anafranil Injection (Alfresa Pharma Corporation)

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt.
Due to a dramatic decrease in dosage or discontinuation of administration, withdrawal symptoms such as queasy, headache, malaise, irritability, emotional instability, sleep disorder, and muscle twitching etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

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5 <Psychotropics> Trazodone Hydrochloride

[Brand Name] Desyrel Tablets 25 and 50 (Pfizer Japan Inc.), Reslin Tablets 25 and 50 (Nippon Organon K.K.) and others

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Due to a dramatic decrease in dosage or discontinuation of administration, withdrawal symptoms such as queasy, headache, malaise, anxiety, and sleep disorder etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

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6 <Psychotropics> Nortriptyline Hydrochloride

[Brand Name] Noritren Tablets 10 mg and 25 mg (Dainippon Sumitomo Pharma Co., Ltd.)

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
In tricyclic antidepressants, due to a dramatic decrease in dosage or discontinuation of administration, withdrawal symptoms such as queasy, headache, malaise, irritability, emotional instability, and sleep disorder etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

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7 <Psychotropics> Paroxetine Hydrochloride Hydrate

[Brand Name] Paxil Tablets 10 mg and 20 mg (GlaxoSmithKline K.K.)

[Warning]

WARNING

It has been reported that placebo-controlled clinical trials in patients aged 7-18 years with Major Depressive Disorder (MDD) conducted overseas failed to demonstrate efficacy, and is associated with an increase risk of suicide. Careful consideration should be given when administering this drug in patients with MDD under age of 18.

[Contraindications]	"Patients under age of 18 (patients with MDD)" was omitted.
[Precautions of Indications]	Since it has been reported that antidepressants increased the risk of suicidal ideation and attempts in patients under age of 18, prescribers must balance this risk and benefit in using antidepressants in such patients.
[Careful Administration]	Patients with a history of suicidal ideation or suicide attempts, and patients with suicidal ideation
[Important Precautions]	Since patients with depressive symptoms have a risk of suicidal ideation and suicidal attempts, they should be carefully monitored for their conditions especially at the beginning of a course of treatment, or at the time of dose changes, either increase or decrease. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness are observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken. Additionally, as in the patients with the psychiatric disorders indicated for this drug other than depression/depressed state may also possibly engage in suicide attempts as well as being accompanied with depression/depressed state, administration in such patients should be implemented with close monitoring. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts. Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians. A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may lead to a change to manic state or destabilization of the conditions. Therefore, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Since it has been reported that this drug increased the risk of congenital anomaly in the neonates of the female patients treated with this drug, administration in pregnant women or women with a possible pregnancy should be limited to cases of which the potential benefit outweighs the potential risk.
[Use in pregnant, parturient and nursing women]	**Pregnant etc.:** Administration of this drug in pregnant women or women with a possible pregnancy should be started only if the potential benefit outweighs the risk. Furthermore, in the event pregnancy is discovered during treatment with this drug, either administration should be discontinued or alternative treatment should be implemented unless continuation of administration is evaluated to be appropriate. [This is because some epidemiological survey conducted overseas have suggested that an increase in the risk of congenital anomaly, especially congenital cardiovascular anomaly (ventricular or atrial septal defect, etc.), in the neonates whose mothers received this drug in the first trimester of pregnancy. One of these studies found that approximately 2% whose mothers received this drug in early pregnancy had a cardiovascular anomalies, compared with the normal rate of approximately 1% seen in the general population. Also, symptoms such as respiratory depression, apnoea, cyanosis, polypnoea, epileptiform attacks, tremor, hypotonia or hypertonia, hyperreflexia, twitch, irritability, persisting crying, lethargy, somnolence, pyrexia, hypothermia, feeding disorder, vomiting, and hypoglycemia etc. in the neonates of female patients exposed to this drug in the last stages of pregnancy have been reported. Many of them occurred immediately after or within 24 hours of parturition. Note that there are cases that these symptoms were reported as neonatal asphyxia or drug withdrawal syndrome.]
[Use in Children]	It has been reported that short-term (4-16 weeks) placebo-controlled trials of antidepressant drugs including this drug in patients under the age of 18 years with MDD and other psychiatric disorders conducted overseas have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was approximately 4%,compared with the placebo risk of approximately 2%. No suicides occurred in these trails.
<Reference Information>	Company report

8 <Psychotropics> Maprotiline Hydrochloride

[Brand Name] Ludiomil Tablets 10 mg, 25 mg, and 50 mg (Novartis Pharma K.K.) and others

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Due to a dramatic decrease in dosage or discontinuation of administration, withdrawal symptoms such as queasy, headache, malaise, irritability, emotional instability, sleep disorder, and muscle twitching etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

9 <Psychotropics> Mianserin Hydrochloride

[Brand Name] Tetramide Tablets 10 mg and 30 mg (Nippon Organon K.K.)

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Due to a dramatic decrease in dosage or discontinuation of administration, symptoms of withdrawal such as tremor, feeling irritated, and anxiety etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

10 <Psychotropics> Milnacipran Hydrochloride

[Brand Name] Toledomin Tablets 15 and 25 (Asahi Kasei Pharma Corporation)

[Precautions of Indications] It has been reported that treatment with antidepressants increased the risk of suicidal ideation and attempts in patients under age of 18, prescribers must balance this risk and benefit in using antidepressants in such patients.

[Careful Administration] Patients with a history of suicidal ideation or suicide attempts, and patients with suicidal ideation

[Important Precautions] Since patients with depressive symptoms have a risk of suicidal ideation and suicidal attempts, patients should be carefully monitored for their conditions especially at the beginning of a course of treatment, or at the time of dose changes, either increase or decrease. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken.
Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Use in Children] Tests to verify the efficacy and safety of this drug in children have not been conducted.
It has been reported that short-term (4-16 weeks) placebo-controlled trials of antidepressant drugs including this drug in patients under the age of 18 years with MDD and other psychiatric disorders conducted overseas have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was approximately 4%,compared with the placebo risk

of approximately 2%. No suicides occurred in these trails.
It has been reported that in placebo-controlled clinical trials of paroxetine hydrochloridein in patients aged 7 to 18 with MDD(classified by DSM-IV) conducted overseas,could not confirm the efficacy of the drug compared with the placebo group.

<Reference Information> Company report

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11 <Psychotropics> Pemoline

[Brand Name] Betanamin Tab., Betanamin Tab. 25 mg and 50 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)

[Warning]

WARNING

Periodic haematological examination etc. should be conducted while administering this drug since cases of serious hepatic function disorder leading to fatal outcome have been reported in the post-marketing report in foreign countries.

<Reference Information> Company report

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12 <Psychotropics> Setiptiline Maleate, Dosulepin Hydrochloride, Trimipramine Maleate, Lofepramine Hydrochloride

[Brand Name] Tecipul Tab. (Mochida Pharmaceutical Co., Ltd.) and others
Prothiaden Tablets 25 (Kaken Pharmaceutical Co., Ltd.)
Surmontil Powder 10%, Surmontil Tablets 10 mg and 25 mg (Shionogi & Co., Ltd.)
Amplit Tablets 10 mg and 25 mg (Daiichi Pharmaceutical Co., Ltd.)

[Important Precautions] Caution should be exercised for patients with depression as there is a risk of a suicide attempt. Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Due to a dramatic decrease in dosage or discontinuation of administration, symptoms of withdrawal such as queasy, headache, malaise, irritability, emotional instability, and sleep disorder etc. may occur. The dose should be decreased cautiously and gradually for discontinuation of administration.

<Reference Information> Company report

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13 <Psychotropics> Fluvoxamine Maleate

[Brand Name] Depromel Tablets 25 and 50 (Meiji Seika Kaisha Ltd.), Luvox Tablets 25 and 50 (Solvay Seiyaku K.K.)

[Precautions of Indications] It has been reported that treatment with antidepressants increased the risk of suicidal ideation and attempts in patients under age of 18, prescribers must balance this risk and benefit in using antidepressants in such patients.

[Careful Administration] Patients with a history of suicidal ideation or suicide attempts, and patients with suicidal ideation

[Important Precautions] Since patients with depressive symptoms have a risk of suicidal ideation and suicidal attempts, patients should be carefully monitored for their conditions especially at the beginning of a course of treatment, or at the time of dose changes, either increase or decrease. If the onset or aggravation of self-harm, and emotional lability such as mood fluctuation, akathisia/psychomotor restlessness is observed, the dose should not be increased and appropriate measures, such as tapering-off and discontinuation of treatment, should be taken.

Prescriptions for this drug should be written for the smallest quantity per one prescription for the patients who demonstrate suicidal tendencies, in order to avoid the drug overdose for suicidal attempts.
Families, etc. should be fully advised of the risk such as suicidal ideation and attempts and of the need for close communication with their physicians.

[Use in Children] Tests to verify the efficacy and safety of this drug in children have not been conducted.
It has been reported that short-term (4-16 weeks) placebo-controlled trials of antidepressant drugs including this drug in patients under the age of 18 years with MDD and other psychiatric disorders conducted overseas have revealed a greater risk of suicidal ideation or attempts. The average risk of such events in patients receiving antidepressants was approximately 4%,compared with the placebo risk of approximately 2%. No suicides occurred in these trails. Note that single clinical trial of this product targeting obsessive-compulsive disorder is included in these studies.
It has been reported that in placebo-controlled clinical trials of the similar drug (paroxetine hydrochloride) in patients aged 7 to 18 with MDD(classified by DSM-IV) conducted overseas,could not confirm the efficacy of the drug compared with the placebo group.

<Reference Information> Company report

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14 <Central nervous system agents-Miscellaneous> Riluzole

[Brand Name] Rilutek Tablets 50 (Sanofi-Aventis K.K.)

[Adverse Reactions (clinically significant adverse reactions)] **Hepatic function disorder and jaundice:** Hepatic function disorder with significant increase in AST (GOT), ALT (GPT), γ-GTP, or Al-P levels, etc. and jaundice may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

<Reference Information> Company report

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15 <Antihypertensives> Indapamide

[Brand Name] Tenaxil Tablets 1 mg and 2 mg (Alfresa Pharma Corporation), Natrix Tablets 1 and 2 (Kyoto Pharmaceutical Industries., Ltd.) and others

[Adverse Reactions (clinically significant adverse reactions)] **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme exudativum:** Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme exudativum may occur. Patients should be carefully monitored and if symptoms such as erythema, itching, enanthema are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

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16 <Over the counter drugs> Ephedra Herb/Glycyrrhiza/Apricot Kernel/Stephania Tetrandra/Coix Seed Ephedra Herb/Apricot Kernel/Coix Seed/Glycyrrhiza/Sinomenium Stem/ Animal Bile

[Brand Name] Tsusanto (Saishunkan Co., Ltd.)
Saishun Tsusanto Extract Granules (Saishunkan Co., Ltd.)

[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.

Interstitial pneumonia: Shortness of breath, dyspnoea, pyrexia, etc. occur together with cough.

<Reference Information> Company report

<Over the counter drugs>

17 Drug Product Containing Theophylline or Aminophylline (having dosage and administration for children)

[Brand Name] Aneton Antitussives Granule (Pfizer Japan Inc.), Semper Junior (Taisho Pharmaceutical Co., Ltd.), Save (Kobayashi Pharmaceutical Co., Ltd.), Mircode Tablet (Sato Pharmaceutical Co., Ltd.)
Artar Oral Sol. (Kyowa Pharmaceutical Industry), Asmeton “Strong" (Sankyo Co., Ltd.)

[Consultation] The following patients should consult with a doctor or pharmacist before using the product

Children with pyrexia

Children with a history of convulsion

3

List of products subject to Early Post-marketing Phase Vigilance

(As of February 1, 2006)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Monteplase (Genetical recombination) / Cleactor Injection 400000, 800000, and 1600000[*1]	Eisai Co., Ltd.	August 5 2005
Follitropin Beta (Genetical recombination) / Follistim Inj. 75 and 150	Nippon Organon K.K.	August 11, 2005
Doripenem Hydrate / Finibax 0.25 g IV Solution	Shionogi & Co., Ltd.	September 16, 2005
Dehydrated Ethanol / Anhydrous Ethanol Injection "Fuso"	Fuso Pharmaceutical Industries, Ltd.	September 16, 2005
Dehydrated Ethanol / Dehydrated Ethanol Inj. "Merck"	Merck Hoei Ltd.	September 20, 2005
Pilocarpine Hydrochloride / Salagen Tab. 5 mg	Kissei Pharmaceutical Co., Ltd.	September 22, 2005
Gemtuzumab Ozogamicin (Genetical recombination) / Mylotarg Injection 5 mg	Wyeth K.K.	September 22, 2005
Alteplase (Genetical recombination) / Activacin for Injection 6000000, 12000000, and 24000000[*2]	Kyowa Hakko Kogyo Co., Ltd.	October 11, 2005
Alteplase (Genetical recombination) / Grtpa Inj. 6000000, 12000000, and 24000000[*2]	Mitsubishi Pharma Corporation	October 11, 2005
Candesartan Cilexetil / Blopress Tablets 2, 4, and 8[*3]	Takeda Pharmaceutical Company Limited	October 11, 2005
Moxifloxacin Hydrochloride / Avelox Tablets 400 mg	Bayer Yakuhin, Ltd.	December 9, 2005
Finasteride / Propecia Tablets-0.2 mg and -1 mg	Banyu Pharmaceutical Co., Ltd.	December 14, 2005
Miglitol / Seibule Tab. 25 mg, 50 mg, and 75 mg	Sanwa Kagaku Kenkyusho Co., Ltd.	January 11, 2006
Potassium Clavulanate/Amoxicillin / Clavamox Dry Syrup for Pediatric	GlaxoSmithKline K.K.	January 17, 2006
Paroxetine Hydrochloride Hydrate / Paxil Tablets 10 mg and 20 mg[*4]	GlaxoSmithKline K.K.	January 23, 2006
Ciclosporin / Papilock Mini Ophthalmic Solution 0.1%	Santen Pharmaceutical Co., Ltd.	January 23, 2006
Placental Gonadotrophin / Profasi Injection 5000[*5]	Serono Japan Co., Ltd.	January 30, 2006

Note) Subject to additional indication etc.

*1: An additional indication for “lysis of pulmonary thrombosis of acute pulmonary embolism accompanied with unstable homodynamic”

*2: An additional indication for “the improvement of dysfunction in the acute stage of ischemic cerebrovascular disease (within 3 hours of onset)”

*3: An additional indication for “the treatment of patients in the condition of chromic cardiac failure (mild to moderate) for which administration of angiotensin converting enzyme (ACE) inhibitors is not appropriate”

*4: An additional indication for “obsessive-compulsive disorder”

*5: An additional indication for “induction of spermatogenesis in hypogonadotropic male hypogonadism”