

# Pharmaceuticals and Medical Devices Safety Information

No. 221 January 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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(in the event of inconsistency, the Japanese text shall prevail).*

# Pharmaceuticals and Medical Devices Safety Information No. 221 January 2006

Pharmaceutical and Medical Safety Bureau,  
Ministry of Health, Labour and Welfare, Japan

## [Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	<b>Theophylline etc.</b>	<i>P</i>	<p>Ministry of Health, Labour and Welfare (MHLW) has alerted about the proper use of sustained release oral theophylline by calling for an inclusion of the standard dosage in “Precautions of Dosage and Administration” of the package insert by citing “Japanese Pediatric Guideline for the Treatment and Management of Asthma” by Japan Society of Pediatric Allergy and Clinical Immunology. Careful administration such as blood concentration monitoring and special care for children with a medical history of epilepsy and convulsion, children with pyrexia, and infants under 6 months old have been urged in the pediatric section of “Careful Administration” to call for attention.</p> <p>In response to the recent revision to “Japanese Pediatric Guideline for the Treatment and Management of Asthma” by the Japanese Society of Pediatric Allergy and Clinical Immunology, the outline of the guideline and the revision to PRECAUTIONS section for the use of theophylline etc. is presented.</p>	3
2	<b>Implantable cardiac pacemaker, etc.</b>	<i>P</i>	<p>It is presented that MHLW requested manufacturers to make revisions to the PRECAUTIONS section of the package insert regarding the oversensing during the X-ray irradiation caused by CT apparatus of X-ray.</p> <p>It is also presented that MHLW requested to alert Thera DR-i (Medtronic Japan Co., Ltd.) etc. regarding the reset caused as a result of X-ray irradiation.</p>	12
3	<b>(1) Ibuprofen (and 13 others)</b> <b>(2) Electrosurgical unit (ESU) used for radiofrequency ablation (RFA)</b>		Revision of PRECAUTIONS (No. 172)	16
4	<b>Products subject to Early Post-marketing Phase Vigilance</b>		Lists products subject to Early Post-marketing Phase Vigilance, as of January 1, 2006.	22

*D*: Distribution of Dear Healthcare Professional Letters    *P*: Revision of PRECAUTIONS    *C*: Case Reports

## Proper use of theophylline in childhood asthma

### 1. Introduction

Theophylline is a typical xanthine derivative such as caffeine and theobromine found in nature. Dimethylxanthine derived/isolated from tea leaves was named theophylline by Kossel in 1888. Currently, it is widely used for the treatment of asthma bronchial since the clinical utility of aminophylline (theophylline as active ingredient in body) against acute attack of asthma bronchial has been reported by Hermann et al. in 1937.

Pharmacological action of theophylline has been known for prevention against airway contraction, reduction of airway hypersensitivity, and anti-inflammatory effect etc. as well as bronchodilatation. Metabolism of theophylline is processed in liver, however, it is known that the metabolic rate depends highly on the concomitant diseases such as infectious diseases, diet, concomitant drugs as well as the individual and his/her age. Additionally, it is suggested that the blood concentration should be paid close attention to when theophylline is administered since the effective area of blood concentration of theophylline is narrow.

The adverse reactions of theophylline are often induced by increased theophylline blood concentration. Gastrointestinal symptoms (nausea, vomiting, etc.) and psychoneurotic symptoms (headache, sleep loss, anxiety, and excitement, etc.) as well as convulsion have been known to occur accompanied by increased theophylline blood concentration. Convulsion, consciousness disturbed, acute encephalopathy, rhabdomyolysis, haemorrhage of digestive tract, aplasia pure red cell, anaphylactic shock, hepatic function disorder, jaundice, tachypnoea, and hyperglycaemia may occur and are indicated in the package insert as clinically significant adverse reactions.

As for proper use of theophylline extended release oral dosage forms, since adverse reaction of convulsions in children has been reported particularly often, careful administration such as blood concentration monitoring and special care for children with a medical history of epilepsy and convulsion, children with pyrexia, and infants under 6 months old have been urged in the pediatric section of "Careful Administration" to promote awareness as well as indicating the standard dosage under the section "Precautions of Dosage and Administration" in the package insert by citing "Japanese Pediatric Guideline for the Treatment and Management of Asthma" by the Japanese Society of Pediatric Allergy and Clinical Immunology.

In response to the recent revision of "Japanese Pediatric Guideline for the Treatment and Management of Asthma" by the Japanese Society of Pediatric Allergy and Clinical Immunology, "PRECAUTIONS" of theophylline have been revised. (including aminophylline and choline theophylline of which active ingredient acts as theophylline in the blood upon absorption). Here, the guideline as well as its content of the revision are presented.

## 2. “Japanese Pediatric Guideline for the Treatment and Management of Asthma”

(Extract, revision, edit of the Japanese Society of Pediatric Allergy and Clinical Immunology “Japanese Pediatric Guideline for the Treatment and Management of Asthma”)

### (1) Management of Acute Exacerbations

#### a. Control medications for asthma attacks

Note) chart key

- ① Quick-relief medications [early treatment for acute attacks]
- ② Additional treatment [stepwise treatment in accordance with the patient’s condition]
- ③,④ Subsequent additional treatment [stepwise treatment after ② in accordance with the patient’s condition]

(for under age of 2)

	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
Mild exacerbation	① $\beta_2$ agonist inhalation	① $\beta_2$ agonist inhalation ② $\beta_2$ agonist inhalation repetitive
Moderate exacerbation	① $\beta_2$ agonist inhalation Oxygen inhalation ② Aminophylline i.v. drip infusion Administration of corticosteroid (consideration)	① $\beta_2$ agonist inhalation (repetitive) Administration of oxygen ② (principally hospitalized) Administration of corticosteroid (i.v. injection/oral) Infusion Aminophylline continuous drip infusion (consideration)
Severe Exacerbation	① Administration of corticosteroid $\beta_2$ agonist inhalation Aminophylline i.v. drip infusion Oxygen inhalation, infusion ② Isoproterenol continuous inhalation (consideration)	Hospitalization ① $\beta_2$ agonist inhalation repetitive Administration of oxygen, infusion Corticosteroid i.v. injection ② Isoproterenol continuous inhalation Corticosteroid i.v. repetitive Aminophylline continuous drip infusion (consideration)
Respiratory failure	① Administration of corticosteroid $\beta_2$ agonist inhalation Aminophylline i.v. drip infusion Oxygen inhalation, infusion ② Isoproterenol continuous inhalation ③ Itracheal intubation Artificial respiration (AR)	Hospitalization ① Isoproterenol continuous inhalation Administration of oxygen, infusion Corticosteroid i.v. repetitive ② Itracheal intubation AR control Aminophylline continuous drip infusion (consideration) Anesthetic (consideration)

**(for aged 2 to 5)**

	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
Mild exacerbation	① $\beta_2$ agonist inhalation	① $\beta_2$ agonist inhalation ② $\beta_2$ agonist inhalation repetitive
Moderate exacerbation	① $\beta_2$ agonist inhalation Oxygen inhalation (consideration) ② Aminophylline i.v. drip infusion	① $\beta_2$ agonist inhalation repetitive Oxygen inhalation (consideration) ② Administration of corticosteroid (i.v. injection/oral) and/or aminophylline i.v. drip infusion/continuous drip infusion
Severe exacerbation	① $\beta_2$ agonist inhalation Oxygen inhalation ② Aminophylline i.v. drip infusion Fluid replacement, correction of acidosis ③ Corticosteroid i.v. injection Isoproterenol continuous inhalation (consideration)	Hospitalization ① $\beta_2$ agonist inhalation repetitive Oxygen inhalation, infusion Corticosteroid i.v. injection Aminophylline continuous drip infusion ② Isoproterenol continuous inhalation Corticosteroid i.v. injection repetitive
Respiratory failure	① $\beta_2$ agonist inhalation Oxygen inhalation ② Aminophylline i.v. drip infusion Fluid replacement, correction of acidosis ③ Corticosteroid i.v. injection Isoproterenol continuous inhalation ④ Intratracheal intubation Assisted respiration Artificial respiration (AR)	Hospitalization ① Isoproterenol continuous inhalation Oxygen inhalation, infusion Repetitive corticosteroid i.v. injection Aminophylline continuous drip infusion ② Isoproterenol continuous inhalation (possible escalation of dosage) Correction of acidosis Intratracheal intubation AR control Anesthetics (consideration)

**(for aged 6 to 15)**

	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
Mild exacerbation	① $\beta_2$ agonist inhalation	① $\beta_2$ agonist inhalation ② $\beta_2$ agonist inhalation repetitive
Moderate exacerbation	① $\beta_2$ agonist inhalation Oxygen inhalation (consideration) ② Aminophylline i.v. drip infusion	① $\beta_2$ agonist inhalation repetitive Oxygen inhalation (consideration) ② Administration of corticosteroid (i.v. injection/oral) and/or aminophylline i.v. drip infusion/continuous drip infusion
Severe exacerbation	① $\beta_2$ agonist inhalation Oxygen inhalation ② Aminophylline i.v. drip infusion Fluid replacement, correction of acidosis ③ Corticosteroid i.v. injection Isoproterenol continuous inhalation (consideration)	Hospitalization ① $\beta_2$ agonist inhalation repetitive Oxygen inhalation, infusion Corticosteroid i.v. injection Aminophylline continuous drip infusion ② Isoproterenol continuous inhalation Repetitive corticosteroid i.v. injection
Respiratory failure	① $\beta_2$ agonist inhalation Oxygen inhalation ② Aminophylline i.v. drip infusion Fluid replacement, correction of acidosis ③ Corticosteroid i.v. injection Isoproterenol continuous inhalation ④ Intratracheal intubation Assisted respiration Artificial respiration (AR)	Hospitalization ① Isoproterenol continuous inhalation Oxygen inhalation, infusion Corticosteroid i.v. injection repetitive Aminophylline continuous drip infusion ② Isoproterenol continuous inhalation (possible escalation of dosage) Correction of acidosis Intratracheal intubation AR control Anesthetics (consideration)

b. Standard dosage of aminophylline injection

**Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002**

Age	Initial dose		Maintenance dose
6 months old – under age of 1	Administer 4 – 5 mg/kg over a period of 30 minutes by drip infusion		0.6 mg/kg/hr
Aged 1 – under age of 2			0.8 mg/kg/hr
Aged 2 – under age of 15	(without administration of theophylline) Administer 4 – 6 mg/kg over a period of 30 minutes by drip infusion	(with administration of theophylline) Administer 3 – 4 mg/kg over a period of 30 minutes by drip infusion	0.8 – 1.0 mg/kg/hr

**Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005**

Age	Initial dose		Maintenance dose
6 months old – under age of 1	Administer 3 – 4 mg/kg over a period of 30 minutes by drip infusion. In the case where theophylline etc. is administered, reduce the dose as appropriate in accordance with the type of drug, length of time after the administration, and its dosage.		0.4 mg/kg/hr
Aged 1 – under age of 2			0.8 mg/kg/hr
Aged 2 – under age of 15	(without administration of theophylline) Administer 4 – 5 mg/kg over a period of 30 minutes by drip infusion	(with administration of theophylline) Administer 3 – 4 mg/kg over a period of 30 minutes by drip infusion	0.8 mg/kg/hr

Note) The upper limit of initial dose is 250 mg.  
The dose is calculated by standard body weight.

**(2) Long-term control medications**

a. Plan for long-term control medications

Note) chart key

- ① Standard treatment [drugs used as standard treatment]
- ② Additional treatment [stepwise treatment in accordance with the patient's condition on top of the standard treatment]
- ③ Further additional treatment [stepwise treatment used in accordance with the patient's condition on top of the standard treatment]

**(for under age of 2)**

	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
Step 1 Intermittent	① Pharmacotherapy based on the type of asthmatic attack ② Antiallergic agent (consideration)	① N/A ② Antiallergic agent
Step 2 Mild persistent	① Oral antiallergic agent ② One or combination of the following (consideration) <ul style="list-style-type: none"> <li>• DSCG + <math>\beta_2</math> agonist</li> <li>• Theophylline extended release oral dosage form</li> <li>• Inhaled corticosteroid (consideration)</li> </ul>	① Antiallergic agent ② DSCG inhalation Inhaled corticosteroid
Step 3 Moderate persistent	① Inhaled corticosteroid ② One or combination of the following (consideration) <ul style="list-style-type: none"> <li>• Oral antiallergic agent</li> <li>• DSCG + <math>\beta_2</math> agonist</li> <li>• Theophylline extended release oral dosage form</li> <li>• <math>\beta_2</math> agonist at bedtime</li> </ul>	① Inhaled corticosteroid ② One or combination of the following <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonist</li> <li>• DSCG inhalation</li> <li>• <math>\beta_2</math> agonist (transdermal patch or oral at bedtime)</li> <li>• Theophylline extended release oral dosage form (consideration)</li> </ul>
Step 4 Severe persistent	① Inhaled corticosteroid ② One or combination of the following <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonist</li> <li>• DSCG + <math>\beta_2</math> agonist</li> <li>• Theophylline extended release oral dosage form</li> <li>• <math>\beta_2</math> agonist at bedtime</li> </ul>	① Inhaled corticosteroid One or both of the following <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonist</li> <li>• DSCG inhalation</li> </ul> ② $\beta_2$ agonist (transdermal patch or oral at bedtime) Theophylline extended release oral dosage form (consideration)

Note) In principle, infants under 6 months old are not subject to administration of theophylline extended release oral dosage form.

**(for aged 2 to 5)**

	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
Step 1 Intermittent	① Pharmacotherapy based on the type of asthmatic attack ② Antiallergic agent (consideration)	① Pharmacotherapy based on the type of asthmatic attack ② Antiallergic agent
Step 2 Mild persistent	① One or combination of the following <ul style="list-style-type: none"> <li>• Oral antiallergic agent</li> <li>• DSCG + <math>\beta_2</math> agonist</li> <li>• Theophylline extended release oral dosage form</li> <li>• Inhaled corticosteroid (consideration)</li> </ul>	① Antiallergic agent or inhaled corticosteroid (consideration) ② Theophylline extended release oral dosage form
Step 3 Moderate persistent	① Inhaled corticosteroid ② Combination of the following (consideration) <ul style="list-style-type: none"> <li>• Oral antiallergic agent</li> <li>• DSCG + <math>\beta_2</math> agonist</li> <li>• Theophylline extended release oral dosage form</li> <li>• <math>\beta_2</math> agonist at bedtime (transdermal patch/oral)</li> </ul>	① Inhaled corticosteroid ② One or combination of the following <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonist</li> <li>• DSCG</li> <li>• Theophylline extended release oral dosage form</li> <li>• <math>\beta_2</math> agonist (transdermal patch or oral at bedtime)</li> <li>• Long-acting <math>\beta_2</math> agonist inhaled</li> </ul>
Step 4 Severe persistent	① Inhaled corticosteroid ② Combination of the following <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonist</li> <li>• DSCG + <math>\beta_2</math> agonist</li> <li>• Theophylline extended release oral dosage form</li> <li>• <math>\beta_2</math> agonist at bedtime (transdermal patch/oral)</li> </ul>	① Inhaled corticosteroid One or combination of the following <ul style="list-style-type: none"> <li>• Leukotriene receptor antagonist</li> <li>• DSCG</li> <li>• Theophylline extended release oral dosage form</li> <li>• <math>\beta_2</math> agonist (transdermal patch or oral at bedtime)</li> <li>• Long-acting <math>\beta_2</math> agonist inhaled</li> </ul>

**(for aged 6 to 15)**

	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
Step 1 Intermittent	① Medications based on the type of asthmatic attack ② Antiallergic agent (consideration)	① Medications based on the type of asthmatic attack ② Antiallergic agent
Step 2 Mild persistent	① Inhaled corticosteroid or one or combination of the following • Oral antiallergic agent • DSCG • Theophylline extended release oral dosage form	① Inhaled corticosteroid or antiallergic agent ② Theophylline extended release oral dosage form
Step 3 Moderate persistent	① Inhaled corticosteroid ② Combination of the following (consideration) • Oral antiallergic agent • DSCG • Theophylline extended release oral dosage form	① Inhaled corticosteroid ② One or combination of the following • Leukotriene receptor antagonist • Theophylline extended release oral dosage form • Long-acting $\beta_2$ agonist inhaled • DSCG • Transdermal patch $\beta_2$ agonist
Step 4 Severe persistent	① Inhaled corticosteroid ② Combination of the following • Leukotriene receptor antagonist • DSCG • Theophylline extended release oral dosage form • Long-acting $\beta_2$ agonist (transdermal patch/oral) ③ Oral corticosteroid (consideration)	① Inhaled corticosteroid One or combination of the following • Leukotriene receptor antagonist • Theophylline extended release oral dosage form • Long-acting $\beta_2$ agonist inhaled • DSCG • Transdermal patch $\beta_2$ agonist ② Oral corticosteroid (consideration)

## b. Standard daily dose of theophylline extended release oral dosage form

**(for aged 6 to 15)**

Age	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2002	Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005
6 months old – under age of 1	6 – 8 mg/kg	6 mg/kg
Aged 1 – under age of 2	8 – 10 mg/kg	8 – 10 mg/kg
Aged 2 – 15	10 mg/kg	8 – 10 mg/kg

**(3) Main changes to the description regarding theophylline etc.**

## a. Theophylline extended release oral dosage form

- Changes to the positioning of “Long-term control medication” and to standard daily dose.
- In principle, administration to patients under age of 2 with convulsive disorder is not recommended.
- It is desirable for instruction to be given in advance if temporary dose reduction or discontinuation of administration will be necessary when pyrexia may occur.

## b. Aminophylline injection

- Changes to the positioning of “Handling of Acute Exacerbations” and standard dose.
- In principle, administration to patients under age of 2 with convulsive disorder is not recommended.
- Administration to patients under age of 2 who develop pyrexia should be carefully considered.

## c. Aminophylline suppository

- In principle, this drug should not be used in patients under age of 2 with acute attack as rapid elevation of blood concentration may occur.



- Administration of this drug in patients under age of 2 with regular oral administration of theophylline extended release oral dosage form is not recommended.

### 3. Revision of PRECAUTIONS

#### (1) Reasons for the revisions

The sections of “Precautions of Dosage and Administration” in the package inserts of theophylline extended release oral dosage form (preparation with indication for pediatric), aminophylline injection (preparation with indication for bronchial asthma), and aminophylline suppository have been revised in accordance with the revision of “Japanese Pediatric Guideline for the Treatment and Management of Asthma” by the Japanese Society of Pediatric Allergy and Clinical Immunology by citing the guideline. Additionally, those of other drugs with similar active components have been revised as well.

#### (2) Outline of the revisions

- a. Revised items in accordance with the revision of the guidelines
  - ① Theophylline extended release oral dosage form (preparation without indication for pediatric)
    - Revisions of sections of “Precautions of Dosage and Administration” that are cited from the guidelines.
    - It is added that the measures at the onset of pyrexia should be explained to caregivers etc. in “Important Precautions”.
    - Cautions in dispensing were added to “Precautions in use” to enable temporary dose reduction/discontinuation in case of pyrexia.
  - ② Aminophylline injection (preparation with indication for bronchial asthma)
    - “Precautions of Dosage and Administration” is newly added citing the guideline.
  - ③ Aminophylline suppository
    - “Precautions of Dosage and Administration” is newly added citing the guidelines.
    - It is added that the measures at the onset of pyrexia should be explained to caregivers etc. in “Important Precautions”.
- b. Revised items that are not described in the guidelines
  - ① Theophylline extended release oral dosage form (preparation with indication for pediatric)
    - It is added that the measures at the onset of pyrexia should be explained to caregivers etc. in “Important Precautions”.
  - ② Theophylline injection
    - “Precautions of Dosage and Administration” is newly added based on aminophylline injection (preparation with indication for bronchial asthma) in accordance with the guidelines.
  - ③ Aminophylline oral dosage form
    - It is added that the measures at the onset of pyrexia should be explained to caregivers etc. in “Important Precautions”.
    - Cautions in dispensing were added to “Precautions in use” to enable temporary dose reduction/discontinuation in case of pyrexia.
  - ④ Choline theophylline
    - It is added that the measures at the onset of pyrexia should be explained to caregivers etc. in “Important Precautions”.
    - Cautions in dispensing were added to “Precautions in use” to enable temporary dose reduction/discontinuation in case of pyrexia.
  - ⑤ OTC drugs containing theophylline or aminophylline (preparation with indication for pediatric)
    - “Children with pyrexia, children with a medical history of convulsion” is added to “Consultation”.

#### 4. Conclusion

As the review result of adverse reaction cases of convulsion reported to have occurred in children after administration of theophylline etc. by marketing authorisation holders, cases of noncompliance of the guidelines and administration in pyrexia etc. are often found. When administering theophylline etc. in patients with childhood asthma, patient should be carefully monitored in accordance with the guidelines etc. In particular, administration in infants should be carefully considered as well as conducting careful administration through observation of clinical conditions etc. and blood level monitoring.

#### 5. Theophylline products

##### Ethical drugs

(extract from The List of Prescription Medicine August, 2005 edition)

Nonproprietary name	Brand name (name of company)		
Theophylline	Ardephyllin DS 20%, Ardephyllin Tablets 100 (Sawai Pharmaceutical Co., Ltd.) Slo-bid Granule, Slo-bid Dry Syrup 20%, Slo-bid 100 and 200 (Nippon Hexal Corporation) Cylmin Tablets 100 (Tsuruhara Pharmaceutical Co., Ltd.) Theo-slow Tablets 100 and 200, Theoslow L Tablets 200 and 400 (Kyowa Pharmaceutical Industry Co., Ltd.) Theodur Granules 20%, Theodur Syrup 2%, Theodur Dry Syrup 20%, Theodur Tablets 50 mg, 100 mg, and 200 mg (Mitsubishi Pharma Corporation) Theophylline Dry Syrup 20% "JD" (J-DOLPH Pharmaceutical Co., Ltd.) Teofurmate Dry Syrup 20%, Teofurmate L Tablets 200 and 400 (Towa Pharmaceutical Co., Ltd.) Theolong Granules 50%, Theolong Tablets 50 mg, 100 mg, and 200 mg (Eisai Co., Ltd.) Terdan Dry Syrup 20% for Pediatric, Terdan Tablets 100 and 200, Terdan-L Tablets 200 (Taiyo Yakuhin Co., Ltd.) Telbans Dry Syrup 20% (Medisa Shinyaku Inc.) Flemphyline Tablets 100 and 200 (Taisho Pharmaceutical Industries, Ltd.) Unicon CR Dry Syrup 20%, Unicon Tablets 100, 200, and 400, Sekiroid Tablets 100 (Nichi-Iko Pharmaceutical Co., Ltd.) Uniphyl Tablets 100, 200, and 400 (Otsuka Pharmaceutical Co., Ltd.)		
	Theodrip (Nikken Chemicals Co., Ltd.)		
	Aminophylline	Neophyllin Powder, Neophyllin Tablets (Sannova Co., Ltd.)	
		Albina Suppositories 50, 100, 200, and 400 (Hisamitsu Pharmaceutical Co., Inc.)	
		Anephyllin Intravenous Injection (Maruko Pharmaceutical Co., Ltd.) Aminophylline Injection (Tsuruhara) (Tsuruhara pharmaceutical Co., Ltd.) Aminophylline Intravenous Injection "TOWA" (Towa Pharmaceutical Co., Ltd.) Aminophylline Injection "Hishiyama" (Nipro Pharma Corporation) Aminophylline Intravenous Solution "Mita" (Toyo Phamar Co., Ltd.) Aminophylline Injection 250 mg "NP" (Nipro Pharma Corporation) Aminophylline Injection (Abbott Japan Co., Ltd.) Kyophyllin Injection 2.5% (Kyorin Pharmaceutical Co., Ltd.) Theocardin V "ISEI" (ISEI Co., Inc.) Nichiphyllin Inj. PB, Nichiphyllin Injection (Nisshin Pharmaceutical Co., Ltd.) Neophyllin Injection, Neophyllin Injection in Intravenous Drip Bag 250 mg (Eisai Co., Ltd.) Microfillin Injection 2.5%, Microfillin Injection Syringe 250 mg (Taiyo Yakuhin Co., Ltd.)	
		Choline theophylline	Theocolin Powder, Theocolin Tablets (Sannova Co., Ltd.)

**Products OTC****(preparation with indication for pediatric)**

(extract from JAPIC OTC Drugs in Japan January, 2005 edition)

<b>Nonproprietary name</b>	<b>Brand name (name of company)</b>
Drugs containing theophylline	Aneton Antitussives Granules (Pfizer Japan Inc.) Semper Junior (Taisho Pharmaceutical Co., Ltd.) Save (Kobayashi Pharmaceutical Co., Ltd.) Mircode Tablet (Sato Pharmaceutical Co., Ltd.)
Drugs containing aminophylline	Artar Oral Sol. (Kyowa Pharmaceutical Industry) Asmeton "Strong" (Sankyo Co., Ltd.)

## Impact of X-ray CT apparatus etc. on implantable cardiac pacemaker etc.

### 1. Outline

#### (1) Instruction on the revision of PRECAUTIONS regarding the interactions between X-ray CT apparatus etc. and implantable cardiac pacemaker etc. (PFSB/SD Notification No. 1125001 issued by the director of the Safety Division dated November 25, 2005)

As for implantable cardiac pacemaker manufactured by Medtronic Japan Co., Ltd. (brand name: Medtronic InSync 8040), occurrence of partial electrical resetting (hereinafter called “reset”) etc. due to X-ray irradiation by X-ray CT apparatus has been revealed. Therefore, attention has been called for thorough instruction on revision to PRECAUTIONS of the package insert and “Pharmaceuticals and Medical Devices Safety Information No. 213” described the content.

Also, it has been confirmed that there is a possibility that similar events may occur with other implantable cardiac pacemakers and defibrillators (hereinafter referred to as “implantable cardiac pacemaker etc.”), consequently, the manufacturers have conducted an inspection, resulting in the confirmation that oversensing of implantable cardiac pacemaker etc. of all the manufacturers has been triggered during X-ray irradiation.

Therefore, MHLW had instructed the related manufacturers of implantable cardiac pacemaker, X-ray CT apparatus, and medical devices combined with X-ray CT apparatus (hereinafter called “X-ray CT apparatus etc.”) to make revisions to PRECAUTIONS section of the package insert as well as having taken necessary measures such as promoting awareness in medical institutions etc.

#### (2) Promotion of awareness regarding implantable cardiac pacemaker (Thera series) manufactured by Medtronic Japan Co., Ltd. (PFSB/SD Notification No. 1125005 issued by the director of the Safety Division dated November 25, 2005)

Thera series implantable cardiac pacemaker, “Thera DR-i” by Medtronic Japan Co., Ltd., and similarly constructed “Thera D-i”, “Thera S-i”, “Thera SR-i”, and “Thera VDD-i” (hereinafter called “Thera DR-i etc.”) have been confirmed to exhibit resetting due to X-ray irradiation by X-ray CT apparatus as well as Medtronic InSync 8040.

Therefore, MHLW had instructed Medtronic Japan Co., Ltd. to promote awareness in physicians etc. regarding Thera DR-i etc. to ensure safety of patients in use, as well as having taken necessary measures such as promoting awareness in medical institutions etc.

### 2. Instructions issued to manufacturers

#### (1) Instruction on the revision to PRECAUTIONS section regarding the interactions between X-ray CT apparatus etc. and implantable cardiac pacemaker etc.

1) MHLW had instructed related manufacturers of implantable cardiac pacemaker etc. as follows.

① The following content should be added to “Important Precautions” section of the package insert of implantable cardiac pacemaker etc.

a. Implantable cardiac pacemaker

“When conducting X-ray CT test in patients with this product implanted, caution should be exercised not to irradiate the body with the X-ray beam for more than 5 seconds as pacing output of this product may be temporarily suppressed due to oversensing caused by sequential irradiation of X-ray beam (See the section on “Interactions”).”

b. Implantable defibrillators

“When conducting X-ray CT test in patients with this product implanted, pay sufficient attention not to irradiate the body with X-ray beam as appropriate treatment may be temporarily suppressed or inappropriate pulsation treatment may be conducted due to oversensing caused by sequential irradiation of X-ray beam (See section on “Interactions”).”

- ② X-ray CT apparatus and medical devices combined with X-ray CT apparatus should be added as combination devices to the “Interaction” section of the package insert of implantable cardiac pacemakers etc. with the following table.

a. Implantable cardiac pacemaker

Interactions	Measures to be taken
When conducting CT tests requiring sequential irradiation of X-ray beam, output of the pacing pulse of implantable cardiac pacemakers may be temporarily suppressed due to oversensing caused by influencing the C-MOS IC inside the body.	<ul style="list-style-type: none"> <li>• The body part implanted should not be irradiated for 5 seconds and more by X-ray beam.</li> <li>• Attempt if displacement of the pacemaker out of the irradiation site by “holding both arms up” etc. of the patient is an option, when tests requiring sequential irradiation by X-ray beam on the site implanted for 5 seconds and more cannot be avoided for treatment. If sequential irradiation on the body implanted by X-ray beam for 5 seconds and more still cannot be avoided, set to fixed-pacing mode and avoid competitive pacing as well as monitoring pulse. Or prepare and use temporary extracorporeal pacing.</li> </ul>

b. Implantable defibrillators

Interactions	Measures to be taken
When conducting CT tests requiring sequential irradiation of X-ray beam, output of the pacing pulse of implantable defibrillators may be temporarily suppressed or inappropriate pulsation treatment may be conducted due to oversensing caused by influencing the C-MOS IC inside the body.	<ul style="list-style-type: none"> <li>• The body part implanted should not be irradiated by X-ray beam.</li> <li>• Attempt if displacement of the defibrillators out of the irradiation site by “holding both arms up” etc. of the patient is an option, when test requiring sequential irradiation of X-ray beam on the site implanted cannot be avoided for treatment. If sequential irradiation of X-ray beam on the body implanted still cannot be avoided, monitor pulses during the test upon turning off the tachycardia detector. Or prepare and use temporary extracorporeal defibrillators or pacing.</li> </ul>

- ③ Appropriate measures such as additionally including the content of aforementioned ① and ② on the patient handbook should be taken as similar cautions should be exercised for patients already implanted with an implantable cardiac pacemaker etc.

- 2) MHLW had instructed related manufactures of X-ray CT apparatus etc. to add the following content under the “Important Precautions” section in the package insert of such devices.

“When conducting the tests requiring a sequential irradiation of X-ray beam on the site implanted with an implantable cardiac pacemaker or defibrillators, inappropriate operation may occur in these devices. If irradiation on the site implanted by X-ray cannot be avoided for the test, take appropriate measures by referring to the “Important Precautions” and “Interaction” sections etc. in the package insert of implantable cardiac pacemakers or defibrillators.”

- 3) MHLW had instructed manufacturers of implantable cardiac pacemakers etc. and X-ray CT apparatus to promote awareness regarding the content of aforementioned 1) and 2) in the related healthcare providers.

**(2) Promotion of awareness regarding implantable cardiac pacemakers (Thera series) manufactured by Medtronic Japan Co., Ltd.**

MHLW had instructed Medtronic Japan Co., Ltd. to promote awareness by providing the following items to the physicians and radiological technicians who deal with these devices.

- 1) In principle, X-ray irradiation by X-ray CT apparatus on the site implanted with Thera DR-i etc. in the patients with stimulation threshold 3.5 V and higher or unknown should not be conducted as resetting of Thera DR-i etc. may be triggered.
- 2) Also, when X-ray irradiation on the site implanted with this device is inevitably conducted for treatment, X-ray irradiation should be performed while monitoring the patient's pulse under supervision of the specialists capable of promptly canceling the reset by its programmer if it should occur.
- 3) Furthermore, after X-ray irradiation by X-ray CT apparatus etc. on the site implanted with this device in the patients with stimulation threshold below 3.5 V, check if any abnormalities are caused in Thera DR-i as expeditiously as possible.

### **3. Request for medical institutions**

#### **(1) The interactions between X-ray CT apparatus etc. and implantable cardiac pacemakers etc.**

When using X-ray CT apparatus etc. in patients with implantable cardiac pacemakers etc., proper use of this device is requested with regard to the following items.

- 1) The site implanted with an implantable cardiac pacemaker should not be irradiated for 5 seconds and more by X-ray beam.
- 2) The site implanted with implantable defibrillators should not be irradiated.
- 3) Attempt if displacement of the pacemaker out of the irradiation site by "holding both arms up" etc. of the patient is an option, when tests requiring sequential irradiation by X-ray beam on the site implanted for 5 seconds and more cannot be avoided for treatment. If sequential irradiation on the body implanted by X-ray beam for 5 seconds and more still cannot be avoided, set to fixed-pacing mode and avoid competitive pacing as well as monitoring pulse. Or use upon preparation of temporary extracorporeal pacing.
- 4) Attempt if displacement of the defibrillators out of the irradiation site by "holding both arms up" etc. of the patient is an option, when test requiring sequential irradiation of X-ray beam on the site implanted cannot be avoided for treatment. If sequential irradiation of X-ray beam on the body implanted still cannot be avoided, monitor pulses during the test upon turning off the tachycardia detector. Or use upon preparation of temporary extracorporeal defibrillators or pacing.  
Also, provide sufficient explanation to the patient so that a patient already implanted with this device should not receive an X-ray examination at another institution without knowing the information.

#### **(2) Implantable cardiac pacemakers (Thera series) manufactured by Medtronic Japan Co., Ltd.**

When using X-ray CT apparatus etc. in patients with implantable cardiac pacemakers such as Thera DR-i, proper use of this device is requested with regard to the following items.

- 1) In principle, X-ray irradiation by X-ray CT apparatus on the site implanted with Thera DR-i etc. in the patients with stimulation threshold 3.5 V and higher or unknown should not be conducted as resetting of Thera DR-i etc. may be triggered.
- 2) Also, when X-ray irradiation on the site implanted with this device is inevitably conducted for treatment, X-ray irradiation should be performed while monitoring the patient's pulse under supervision of the specialists capable of promptly canceling the reset by its programmer if it should occur.

- 3) Furthermore, after X-ray irradiation by X-ray CT apparatus etc. on the site implanted with this device in the patients with stimulation threshold below 3.5 V, check if any abnormalities are caused in Thera DR-i as expeditiously as possible.

Also, provide sufficient explanation to the patient to ensure that patient already implanted with this device does not carelessly receive an X-ray examination at another institution.

# 3

## Revision of PRECAUTIONS (No. 172)

### (1) Drugs, etc.

This section presents details of the 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. 220), together with reference materials.

#### 1 <Antipyretics and analgesics, anti-inflammatory agents> Ibuprofen

**[Brand Name]** Brufen Granules, Brufen Tablets 100 and 200 (Kaken Pharmaceutical Co., Ltd.), Unipron Supp. 50 and 100 (Showa Yakuhin Kako Co., Ltd.), and others

**[Adverse Reactions (clinically significant adverse reactions)]** **Acute renal failure, nephritis interstitial, nephrotic syndrome:** Acute renal failure, nephritis interstitial, and nephrotic syndrome may occur. Patients should be carefully monitored and if abnormalities such as oliguria, haematuria, proteinuria, BUN increased, blood creatinine increased, hyperkalaemia, and hypoalbuminaemia are observed, discontinue administration and take appropriate measures.

**Asthmatic attack:** Asthmatic attack may be triggered. If symptoms such as wheezing and dyspnoea are observed, discontinue administration and take appropriate measures.

**<Reference Information>** Company report

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

**[Brand Name]** Soleton Tablets 80 (Nippon Chemiphar Co., Ltd.), Peon Tablets 80 (Zeria Pharmaceutical Co., Ltd.), and others

**[Adverse Reactions (clinically significant adverse reactions)]** **Peptic ulcer, small intestine ulcer, large intestinal ulcer, colitis haemorrhagic:** Peptic ulcer, small intestine ulcer, large intestinal ulcer (may be accompanied by haemorrhage or perforation), and colitis haemorrhagic may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

**<Reference Information>** Company report

#### <Psychotropics>

#### 3 Chlorpromazine Hydrochloride, Chlorpromazine Hydrochloride/Promethazine Hydrochloride/Phenobarbital, Chlorpromazine Hibenstate, Chlorpromazine Phenolphthalinate

**[Brand Name]** Wintermin Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg (Shionogi & Co., Ltd.), Contomin Sugar-coated Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg, Contomin Intramuscular Injection 10 mg, 25 mg, and 50 mg (Mitsubishi Pharma Corporation), and others  
Vegetamin Tablets-A and -B (Shionogi & Co., Ltd.)  
Contomin Powder 10%, Contomin Granules 10% (Mitsubishi Pharma Corporation)  
Wintermin Fine Granules (10%) (Shionogi & Co., Ltd.)



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

**Sudden death, ventricular tachycardia:** Since blood pressure decreased and electrocardiogram abnormal (QT prolongation, T wave flattened, inverted T waves, occurrence of bimodal T wave or U wave) followed by sudden death and ventricular tachycardia (including Torsades de pointes) have been reported, discontinue administration especially if any changes observed in QT intervals. Also, it has been reported that electrocardiogram abnormal during the administration of phenothiazine compound have often been seen in cases administered at a high dose.

**Tardive dyskinesia, dystonia tarda:** Long-term administration may cause movements involuntary such as tardive dyskinesia and dystonia tarda. These symptoms may persist after discontinuation of administration.

**Rhabdomyolysis:** Rhabdomyolysis may occur. Caution should be exercised when CK (CPK) increased, myoglobin blood increased, and myoglobin urine increased, etc.

<Reference Information> Company report

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4 <Psychotropics>

**Levomepromazine Hydrochloride, Levomepromazine Maleate**

**[Brand Name]** Hirnamin Injection (Shionogi & Co., Ltd.), Levotomin Intramuscular Injection 25 mg (Mitsubishi Pharma Corporation)  
Hirnamin Powder 50%, Hirnamin Fine Granules 10%, Hirnamin Tablets (5 mg), (25 mg), and (50 mg) (Shionogi & Co., Ltd.), Levotomin Powder 10% and 50%, Levotomin Granules 10%, Levotomin Tablets 5 mg, 25 mg, and 50 mg (Mitsubishi Pharma Corporation), and others

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

**Tardive dyskinesia, dystonia tarda:** Long-term administration may cause movements involuntary such as tardive dyskinesia and dystonia tarda. These symptoms may persist after discontinuation of administration.

**Rhabdomyolysis:** Rhabdomyolysis may occur. Caution should be exercised when CK (CPK) increased, myoglobin blood increased, and myoglobin urine increased, etc.

<Reference Information> Company report

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5 <Cardiotonics>

**Aminophylline (oral dosage form), Choline Theophylline**

**[Brand Name]** Neophyllin Powder, Neophyllin Tablets (Sannova Co., Ltd.)  
Theocolin Powder, Theocolin Tablets (Sannova Co., Ltd.)

**[Important Precautions]** When the drug is administered to children, especially infants, it is advisable that the parents be instructed in advance to take actions such as temporarily decreasing the dosage or discontinuing the drug in the case that pyrexia is observed.  
When the drug is used for children, due to their general inability to complain of subjective symptoms, parents should be advised to observe their condition carefully, and if any abnormality is observed, report this immediately to the physician, or take other appropriate measures.

6 <Cardiotonics>

**Aminophylline (injectable dosage form), (preparations with the indication for pediatric)**

**[Brand Name]** Neophyllin Injection, Neophyllin Injection in Intravenous Drip Bag 250 mg (Eisai Co., Ltd.), and others

**[Precautions of Dosage and Administration]** Please refer to the Guidelines and other relevant updates for the recommended dosage and regimen for the use of this drug in bronchial asthma in children.

<Reference Information> The Japanese Society of Pediatric Allergy and Clinical Immunology: Japanese Pediatric Guidelines for the Treatment and Management of Asthma 2005

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<Bronchodilators>

**7 Aminophylline (suppository)**

**[Brand Name]** Albina Suppositories 50, 100, 200, and 400 (Hisamitsu Pharmaceutical Co., Inc.)

**[Precautions of Dosage and Administration]** Please refer to the Guidelines and other relevant updates for the regimen for the use of this drug in bronchial asthma in children.

**[Important Precautions]** When the drug is administered to children, especially infants, it is advisable that the parents be instructed in advance to take actions such as temporarily decreasing the dosage or discontinuing the drug in the case that pyrexia is observed.  
When the drug is used for children, due to their general inability to complain of subjective symptoms, parents should be advised to observe their condition carefully, and if any abnormality is observed, report this immediately to the physician, or take other appropriate measures.

**<Reference Information>** The Japanese Society of Pediatric Allergy and Clinical Immunology: Japanese Pediatric Guidelines for the Treatment and Management of Asthma 2005

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<Bronchodilators>

**8 Theophylline (extended release oral dosage form), (preparations with the indication for pediatric)**

**[Brand Name]** Theodur Granules 20%, Theodur Tablets 50 mg and 100 mg, Theodur Syrup 2%, Theodur Dry Syrup 20% (Mitsubishi Pharma Corporation), and others

**[Precautions of Dosage and Administration]** This product should be carefully administered with observing clinical conditions and monitoring of blood theophylline concentration.  
When this product is administered to children with bronchial asthma, the dosage and administration method should be determined by referring to the latest information such as Guidelines of academic societies, etc.

**[Important Precautions]** When this product is administered to children, especially to infants, prescribing persons are recommended to instruct the guardian beforehand to reduce the dose or discontinue the administration of the product temporarily, etc. if the patient develop fever.  
In general, children have inferior ability to complain of subjective symptoms. Before this product is administered, prescribing persons should instruct the guardian to observe the children's conditions and to take appropriate measures such as prompt contact to the physician if any abnormality is observed.

**<Reference Information>** The Japanese Society of Pediatric Allergy and Clinical Immunology: Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005

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<Bronchodilators>

**9 Theophylline (extended release oral dosage form), (preparations without the indication for pediatric)**

**[Brand Name]** Uniphyl Tablets 100 mg, 200 mg, and 400 mg (Otsuka Pharmaceutical Co., Ltd.), and others

**[Important Precautions]** When the drug is administered to children, especially infants, it is advisable that the parents be instructed in advance to take actions such as temporarily decreasing the dosage or discontinuing the drug in the case that pyrexia is observed.  
When the drug is used for children, due to their general inability to complain of subjective symptoms, parents should be advised to observe their condition carefully, and if any abnormality is observed, report this immediately to the physician, or take other appropriate measures.

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10 <Bronchodilators>

## 10 Theophylline (injectable dosage form)

[Brand Name] Theodrip (Nikken Chemicals Co., Ltd.)

[Precautions of Dosage and Administration] Please refer to the Guidelines and other relevant updates for the recommended dosage and regimen for the use of this drug in bronchial asthma in children.

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11 <Antidiabetic agents>

## 11 Glimepiride

[Brand Name] Amaryl Tablets 1 mg and 3 mg (Aventis Pharma Limited)

[Adverse Reactions (clinically significant adverse reactions)] **Haemolytic anaemia, agranulocytosis, pancytopenia:** Haemolytic anaemia, agranulocytosis, and pancytopenia may occur. Patients should be carefully monitored and if abnormalities are observed, discontinue administration and take appropriate measures.

<Reference Information> Company report

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12 <Antineoplastics-Miscellaneous>

## 12 Arsenic Trioxide

[Brand Name] Trisenox Injection 10 mg (Nippon Shinyaku Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Pancytopenia, agranulocytosis, leucopenia:** Pancytopenia, agranulocytosis, and leucopenia may occur. Patients should be carefully monitored and if abnormalities are observed, appropriate measures should be taken.

<Reference Information> Company report

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

## 13 Cefcapene Pivoxil Hydrochloride (fine granule for pediatric use), Cefditoren Pivoxil (fine granule for pediatric use), Cefteram Pivoxil (fine granule for pediatric use)

[Brand Name] Flomox Fine Granules 100 mg for Children (Shionogi & Co., Ltd.)  
Meiact MS Fine Granules for Pediatric (Meiji Seika Kaisha, Ltd.)  
Tomiron Fine Granules for Pediatric 100 (Toyama Chemical Co., Ltd.), and others

[Important Precautions] Decreased serum carnitine with metabolism/excretion of pivalic acid (metabolite of antibiotics with a pivoxil group) due to administration of antibiotics with a pivoxil group including this product (cefcapene pivoxil hydrochloride hydrate, cefditoren pivoxil, cefteram pivoxil) has been reported. In addition, the occurrence of hypoglycemia associated with hypocarnitinemia in infants due to prolonged administration of antibiotics with a pivoxil group alone or by switching has been reported. Therefore, care should be taken about decreased carnitine in the administration of antibiotics with a pivoxil group.

[Adverse Reactions (clinically significant adverse reactions)] **Hypoglycemia associated with hypocarnitinemia:** The occurrence of hypoglycemia associated with hypocarnitinemia in infants due to prolonged administration of antibiotics with a pivoxil group has been reported. If hypoglycemic symptoms, such as convulsion and disturbance of consciousness, occur, the therapy should be discontinued and appropriate measures should be taken.

<Reference Information> Company report

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**Live Bacillus of Calmette and Guerin (BCG)/Connaught Strain**

<b>[Brand Name]</b>	Immucyst Intravesical (Nippon Kayaku Co., Ltd.)
<b>[Adverse Reactions (clinically significant adverse reactions)]</b>	<b>Renal failure:</b> <u>Renal failure may occur. Patients should be carefully monitored through periodic testing for renal function. If abnormalities are observed, discontinue administration and conduct diagnostic test for disseminated BCG infection and take appropriate measures immediately as well as conducting antituberculosis therapy.</u>
<b>&lt;Reference Information&gt;</b>	Company report

**(2) Medical devices**

This section presents details of revisions to the PRECAUTIONS section of package inserts that have been revised according to the Notifications after the previous bulletin (Pharmaceuticals and Medical Devices Safety Information No. 220) (excluding those presented in “2. Impact of X-ray CT apparatus on implantable cardiac pacemaker etc.” of this Bulletin), together with reference materials.

**1 Electrosurgical units (ESU) used for radiofrequency ablation (RFA\*)**

\* RFA: abbreviation for radiofrequency ablation

<b>[Warning]</b>	<p>Hepatic rupture may occur due to the increase of intrahepatic pressure during ablation. Caution should be exercised when treating patients with rapidly increased output or prolonged ablation.</p> <p>Since disseminated recurrent metastasis may be developed due to the tumor tissue not being sufficiently cauterized, periodic testing should be performed after the ablation.</p> <p>Since serious adverse events such as gastrointestinal perforation, perforation bile duct, and injury of posterior intercostal arteries due to inappropriate centesis have been reported, Extra caution should be exercised when operating the device on the hepatic surface or proximal to bile duct.</p>
<b>[Important Precautions]</b>	Physicians should be encouraged to fully understand the therapeutic principles and features of this device and trained for in advance. This device should be used carefully through constant monitoring of energy output and image etc.
<b>[Adverse Event]</b>	<p>Hepatic rupture</p> <p>Metastatic or recurrence after ablation</p> <p>Perforation of neighboring tissues or vessels</p> <p>Peritonitis, sepsis</p>
<b>&lt;Reference Information&gt;</b>	<p>Research report</p> <ol style="list-style-type: none"> <li>1) Kotoh K, Nakamuta M, Morizono S, Kohjima M, Arimura E, Fukushima M, Enjoji M, Sakai H and Nawata H: A multi-step, incremental expansion method for radio frequency ablation: optimization of the procedure to prevent increases in intra-tumor pressure and to reduce the ablation time, Liver International; 2005; 25; 542-547</li> <li>2) Tito Livraghi, Luigi Solbiati, M.Franca Meloni, G. Scott Gazelle, Elkan F.Halpern and S. Nahum Goldberg: Treatment of Focal Liver Tumors with Percutaneous Radio-frequency Ablation: Complications Encountered in a Multicenter Study; Radiology; 2003; 226; 2; 441-451</li> <li>3) Yasushi Imamura, Kazunori Obara, Toshihiko Shibata, Yoshiro Baba, Kenji Tahara, Osamu Kubozono: Two cases of hepatocellular carcinoma showing rapid progression after radio-frequency ablation therapy, Journal of the Japanese Society of Gastroenterology, 2002; 99; 40-44</li> <li>4) Josep M. Llovet, Ramon Vilana, Concepció Brú, Lluís Bianchi, Joan Manuel Salmeron, Loreto Boix, Sergi Ganau, Margarita Sala, Mario Pagès, Carmen</li> </ol>

- Ayuso, Manel Solè, Joan Rodés and Jordi Bruix: Increased Risk of Tumor Seeding After Percutaneous Radiofrequency Ablation for Single Hepatocellular Carcinoma: *Hepatology*; 2001; 33; 1124-1129
- 5) Motoki Nakai, Tatsuya Shiraki, Katsuhiko Azuma, Masako Maeda, Shinya Maeda, Nozomi Takeuchi, Masashi Kimura, Masaki Terada, Morio Sato: Low-output Radiofrequency Ablation Combined with Transcatheter Arterial Oily-chemoembolization for Hepatocellular Carcinoma, *NIPPON ACTA RADIOLOGICA*, 2005; 65; 124-125
- 6) Toshihiko Kawasaki, Masatoshi Kubo, Hobyung Chung and Yasunori Minami: Hepatocellular carcinoma that ruptured during radiofrequency ablation therapy: *Journal of Gastroenterology*; 2004; 39; 1015-1016

# 4

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

(As of January 1, 2006)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Luliconazole ----- Lulicon Cream 1%, Lulicon Solution 1%	POLA Chemical Industries, Inc.	July 20, 2005
Fludeoxyglucose ----- FDGscan Injectable	Nihon Medi-Physics Co., Ltd.	August 1, 2005
Fludeoxyglucose ----- FDGscan-MP Injectable	The Medical and Pharmacological Research Center Foundation	August 1, 2005
Monteplase (Genetical recombination) ----- Cleactor Injection 400000, 800000, and 1600000* <sup>1</sup>	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* <sup>2</sup>	Kyowa Hakko Kogyo Co., Ltd.	October 11, 2005
Alteplase (Genetical recombination) ----- Grtpa Inj. 6000000, 12000000, and 24000000* <sup>2</sup>	Mitsubishi Pharma Corporation	October 11, 2005
Candesartan Cilexetil ----- Blopres Tablets 2, 4, and 8* <sup>3</sup>	Takeda Pharmaceutical Company Limited	October 11, 2005
Moxifloxacin Hydrochloride ----- Avelox Tablets 400 mg	Bayer Yakuin, Ltd.	December 9, 2005
Finasteride ----- Propecia Tablets 0.2 mg and 1 mg	Banyu Pharmaceutical Co., Ltd.	December 14, 2005

Note) Subject to additional indication, etc.

- \*1: An additional indication for “lysis of pulmonary thrombosis of acute pulmonary embolism accompanied with unstable hemodynamic”
- \*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 chronic cardiac failure (mild to moderate) for which administration of angiotensin converting enzyme (ACE) inhibitors is not appropriate”