Pharmaceuticals and Medical Devices Safety Information

No. 237 June 2007

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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. 237 June 2007

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

[Outline of Information]

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1	**The effect from RFID devices in UHF band and mobile phone terminals with a new system on implantable medical devices such as cardiac pacemakers etc.**		MHLW has alerted healthcare providers about the effects on implantable medical devices etc. by various devices using electromagnetic waves in the past issues of Pharmaceuticals and Medical Devices Safety Information. As a result of studies on electromagnetic waves emitted from UHF band RFID devices and W-CDMA mobile phone terminals in the 1.7 GHz band, partial amendments have been made and released in the "Guidelines for Preventing the Effects of Electromagnetic Waves From Various Types of Equipment on Implantable Medical Devices". In this bulletin, MHLW has introduced details of the studies and has promoted awareness.	3
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D: Distribution of Dear Healthcare Professional Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

1

The effect from RFID devices in UHF band and mobile phone terminals with a new system on implantable medical devices such as cardiac pacemakers etc.

MHLW has alerted healthcare providers about the effects on implantable cardiac pacemakers and implantable cardioverter defibrillators (ICDs) (hereinafter referred to as "implantable medical devices etc.") by various devices using electromagnetic waves in the Pharmaceuticals and Medical Devices Safety Information No. 136 (March 1996 edition), No. 137 (May 1996 edition), No. 143 (June 1997 edition), No. 155 (June 1999 edition), No. 173 (January 2002 edition), No. 179 (July 2002 edition), No. 190 (June 2003 edition), No.203 (July 2004 edition), No. 216 (August 2005 edition), and No. 226 (June 2006 edition).

Ministry of Internal Affairs and Communications (MIC) has been implementing "Studies on the Effects of Electromagnetic Waves on Medical Device" since 2000. MIC has been recently conducting studies on the effect of electromagnetic waves of UHF band RFID devices[*1] (hand-held type, fixed type, and built-in type) and W-CDMA mobile phone terminals of 1.7 GHz band on implantable medical devices such as implantable cardiac pacemakers. As a result, on April 24, 2007, partial amendments have been made and released in the "Guidelines for Preventing the Effects of Electromagnetic Waves From Various Types of Equipment on Implantable Medical Devices" (hereinafter referred to as "Guidelines"). In this bulletin, MHLW has introduced details of the studies conducted by MIC and has promoted awareness in patients with implantable medical device through the healthcare providers.

The reports etc. on this investigation by MIC are available on MIC's website under "the Results of a Study on the Effects of Electromagnetic Waves on Medical Device [http://www.soumu.go.jp/s-news/2007/070424_5.html] (in Japanese)".

1. History

This bulletin has described the effect of electromagnetic waves emitted from RFID devices and mobile phone terminals etc. on the implantable medical devices. As for RFID devices, those types using frequency of UHF band have already been released in the market since 2005. Moreover, mobile phone terminals with new systems and models have been released in the market since the previous studies conducted in 2005. In response to MIC's publicized result of the studies on the effect of the electromagnetic waves emitted from RFID devices using UHF band and W-CDMA mobile phone terminals in 1.7 GHz band on implantable medical devices, MHLW will introduce details of the studies to medical institutions, healthcare professionals, and manufacturers of medical devices, etc.

2. Overview of the study

The study was conducted under conditions that the effect on the currently used typical models of the implantable medical devices[*2] by electromagnetic wave delivered from the typical models of RFID devices using UHF band and W-CDMA mobile phone terminals in 1.7 GHz band[*2] were considered maximized.

(1) The effect of electromagnetic waves from RFID devices using UHF band on the implantable medical device.

① The effect of fixed-type RFID devices on the implantable medical devices

- Implantable cardiac pacemaker
  Potential cases of reversible effects by some models of "high output passive tag systems in the 950 MHz band[*3]" among the fixed-type RFID devices, such as "persisting palpitations and dizziness etc. which can be recovered by the patients' own actions such by leaving the place" have been occurred at a maximum distance of 75 cm.
- ICD
  It was confirmed that unnecessary defibrillation shock[*4] may be caused at maximum distance of 10 cm.

② The effect of hand-held type RFID devices on the implantable medical devices
No effects were confirmed.

③ The effect of built-in type RFID devices on the implantable medical devices
No effects were confirmed.

(2) The effect of electromagnetic waves from W-CDMA mobile phone terminals in 1.7 GHz band on the implantable medical devices

- Implantable cardiac pacemaker
  It was confirmed that the effect may be caused at maximum distance of less than 1 cm.
- ICD
  No effects were confirmed.

3. Outline of Amendment of the Guidelines

The following guidelines were added in order to ensure that there will not be any effects from electromagnetic waves emitted from the high output passive tag systems in the 950 MHz band of the fixed-type RFID on implantable cardiac pacemakers.

Fixed-type RFID devices (high output passive tag systems in the 950 MHz band)

① Any person with an implantable medical device should not come close within a radius of 1 meter from the area where fixed-type RFID devices (high output passive tag system in the 950 MHz band) are installed and where RFID stickers (combination of Figures 1 and 2) are attached.

② Any person with implantable medical device should immediately consult his/her physician if he/she feels any change in the physical condition.

③ Relevant organizations should conduct further safety investigations in order to reduce the effects of fixed-type RFID devices (high output passive tag systems in the 950 MHz band) on implantable medical devices.

Figure 1. RFID sticker

Figure 2. Fixed-type RFID sticker
(high output passive tag systems in the 950 MHz band)

4. Request for healthcare providers

It is requested that people with implantable medical device should be informed about the content of these amendments and the following precautions. Caregivers should also be thoroughly instructed if the patient is a child.

●Precautions for people with implantable medical device

(1) RFID devices

① Fixed-type RFID devices (limited to high-power passive tag systems in the 950 MHz band)

As for RFID devices using UHF band, "People with implantable medical device should not come close within a radius of 1 meter from the area where fixed-type high output passive tag systems in the 950 MHz band are installed" has been added in the guidelines. This amendment was based on the results of the study conducted under severe conditions, with the sensitivity of the implantable medical device set at the highest levels that differ from normal condition of use. No cases of malfunction in which effects on the implantable medical devices were observed under normal conditions have been reported. Additionally, this particular device is primarily used for the purpose of batch read-operation of the tags attached to containers and pallets etc. for storing, premises operations, and transportation. Currently, use of the device is limited in places such as warehouse etc. Based on the aforementioned circumstances, the immediate possible effect in daily life is considered extremely low, however, MHLW requests as a prophylactic measure, not come close within a radius of 1 m from the RFID devices with the stickers of the **figures 1 and 2** attached. Information on the installation sites etc. is available on the websites of MIC [http://www.soumu.go.jp/] and Japan Automatic Identification Systems Association (JAISA) [http://www.jaisa.or.jp/] etc.

It is also requested that any person with implantable medical device should immediately consult his/her physician if he/she feels any change in the physical condition around the applicable RFID devices.

② Hand-held, fixed-type (excluding high-power passive tag systems in the 950 MHz band), and built-in type RFID devices

As it is stated as "keep it approximately 22 cm away from the area where the implantable cardiac pacemaker is implanted", in accordance with the guidelines issued based on the result of the studies conducted in 2005, take the same precautions for conventional RFID devices.

(2) Mobile phone terminal

As there were no revisions of the guidelines based on this investigation, it is requested to continue following the existing guidelines (22 cm).

Table 1 Outline of current amendment of the guidelines regarding implantable medical device and various types of devices using electromagnetic waves

<table>
<tr><th colspan="3"></th><th>Conventional guidelines</th><th>Revised guidelines</th></tr>
<tr><td colspan="3">Mobile phone terminals</td><td>Keep a distance of approximately 22 cm and more</td><td rowspan="2">(No changes)</td></tr>
<tr><td colspan="3">RFID devices (exclusive of the following frequency band)</td><td>Keep a distance of approximately 22 cm and more</td></tr>
<tr><td rowspan="4">UHF band RFID devices</td><td rowspan="2">Fixed type</td><td>High output passive tag systems in the 950 MHz band</td><td rowspan="4">--</td><td>Keep a distance of 1 m and more</td></tr>
<tr><td>Excluding the above</td><td rowspan="3">Keep a distance of approximately 22 cm and more</td></tr>
<tr><td colspan="2">Hand-held type</td></tr>
<tr><td colspan="2">Built-in type</td></tr>
</table>

<Reference Information>

*1 RFID (Radio Frequency Identification) device: A device that uses non-contact communications between a tag fitted with an IC and a reader/writer to read and write the data on the tag. It is used in a wide variety of fields, including distribution, inventory control, and settlement of products, etc.
Furthermore, the following types of device exist based on reader/writer configuration:

- Gate type: the reader/writer is established in a gate configuration

- Hand-held type: the reader/writer is a hand-held device that can be carried around
- Fixed type: the reader/writer is used in a stationary condition
- Built-in type: the reader/writer is built-into a printer etc.

*2 Wireless device and implantable medical device used in the studies

① Wireless device

The following models were studied.

- UHF band (950 MHz band) RFID: 17 models
- W-CDMA mobile phone terminal in the 1.7 GHz band: 1 model

Note: List of types (17 models) used in the studies
Hand-held type: 3 models Fixed type: 12 models Built-in type: 2 models
Note that the types where gates are configured by placing antenna are included in the fixed type in this study.

② Implantable medical device

The study covered typical models of implantable cardiac pacemakers and ICDs currently in use.

- Implantable cardiac pacemakers: 31 models
- ICDs: 14 models

*3 High output passive tag systems in the 950 MHz band: A RFID device that uses frequencies (950 MHz) in the UHF band that enable comparatively long distance communications. For example, such system is expected to be used in applications such as for reading all of the attached tags in a container or on a pallet at one time.

*4 Unnecessary defibrillation shock: A phenomenon that occurs where the defibrillating function of the ICD activates without actual ventricular fibrillation.

5. Others

MHLW introduces the attached “Guidelines For Preventing The Effects of Electromagnetic Waves From Various Types of Equipment on Implantable Medical Devices” issued dated on April 2007 based on the results of the studies implemented in 2006 or before by MIC, for reference.

Attachment

Guidelines for Preventing the Effects of Electromagnetic Waves from Various Types of Device on Implantable Medical Devices

April 2007
Ministry of Internal Affairs and Communications (MIC)

In recent years, various types of wireless systems such as mobile phones have been playing an important role in our daily life and there are increasing opportunities for the devices that emit electromagnetic waves to be used near us. Devices which emit electromagnetic waves (hereinafter referred to as "device using electromagnetic waves") include PHS terminals, wireless card (non-contact IC card) systems, electronic article surveillance (EAS) devices, RFID devices (reader of the electronic tags), wireless LANs etc. other than mobile phone terminals, and when these devices come close to electric/electronic devices, effects may occur including malfunction in the electric/electronic devices due to the electromagnetic waves emitted from the device using electromagnetic waves.

Among the electric/electronic devices, as for the implantable medical device such as cardiac pacemakers which are implanted in the body, it is important to prevent effects by sharing the information regarding the occurrence/prevention of the effects among the users of the devices using electromagnetic waves, people with implantable medical devices, and manufacturers of these devices since an adverse health effect may occur when malfunction is caused by electromagnetic waves emitted from the device using electromagnetic waves.

The "Guidelines for the usage of mobile phone terminals etc. for preventing the effects of electromagnetic waves on medical devices", which are also applied to medical electric devices in medical institutions, were established in 1997 by the Conference for Countermeasures for the Issues of Unnecessary Electromagnetic Waves (consisting of academic experts, related ministries and agencies, and related industrial associations etc; current Electromagnetic Compatibility Conference Japan (EMCC); secretariat: Association of Radio Industries and Businesses (ARIB)) for information regarding occurrence/prevention of the effects on implantable medical devices. In view of the use of mobile phone terminals with new systems and recent expansion of use of new devices using electromagnetic waves, MIC has been conducted the studies on the effects of electromagnetic waves from various types of device on implantable medical devices and publicized the results. In August 2005, the Guidelines for Preventing the Effects of Electromagnetic waves from Various Types of Device on Implantable Medical Devices was established based on the results of the studies conducted by FY2004. Later, the guidelines were reviewed in accordance with the results of the study on W-CDMA mobile phone terminal in the 800 MHz band and study on W-CDMA mobile phone terminal in the 1.7 GHz band and RFID devices in the UHF band, conducted in FY2005 and FY2006, respectively.

In conducting the studies, with the cooperation of the related organizations, etc, MIC selected the target encompassing typical models marketed at the time of the studies. However, all the models on the market were not covered, and new models may be marketed after the studies. Moreover, although MIC has conducted the studies using the method considered to be appropriate by the experts, not all the environmental conditions etc. were considered. Therefore, these aforementioned points should be taken into careful consideration when using the guidelines.

MIC will review the guidelines as necessary to improve/maintain the safe and secure electromagnetic wave environment. It is important for users of the devices using electromagnetic waves and people with implantable medical devices to refer to the guideline or other beneficial information to prevent the effects. Additionally, it is important for manufacturers of the devices using electromagnetic waves or implantable medical devices to make efforts to prevent the effects by developing/manufacturing devices that do not emit unnecessarily high electromagnetic waves and/or devices highly functional of eliminating the effect of electromagnetic waves. Furthermore, the related parties should make efforts to share the information beneficial for prevention of the effects by promoting awareness of the information etc.

1 Guidelines for preventing the effects of electromagnetic waves from mobile phone terminals and PHS terminals on implantable medical devices

A Any person with an implantable medical device should keep mobile phone terminals at least approximately 22 cm away from the area where the device is implemented when using or carrying the mobile phone terminal.
Take adequate attention in crowded place as mobile phone terminals may be used nearby.

B Any person with an implantable medical device should handle PHS terminals in the same way as the mobile phone terminals mentioned in A above.

(As the implantable medical device is not completely unaffected when PHS terminals are brought closely, and distinguishing between PHS terminals and mobile phone terminals by appearance is not easy, it is desirable to treat the PHS terminals in the same manner as the mobile phone terminals for careful handling.)

C It is desirable for people carrying mobile phone terminals or PHS terminals to turn them off in areas where there is a possibility of being close proximity to a person with an implantable medical device (e.g. in crowded trains).

2 Guidelines for preventing the effects of electromagnetic waves from wireless card (non-contact IC card) systems on implantable medical devices (note)

A Any person with a cardiac pacemaker should keep the reader/writer (antenna) of a wireless card system approximately at least 12 cm away from the area where the device is implemented.

B Although it is not necessary for person with ICD to be specifically conscious of the wireless card systems in daily life, close contact of the reader/writer (antenna) of the wireless card system with the area where the device is implanted should be avoided.

C As for the manufacturers of wireless card systems, it is effective to make the reader/writer (antenna) parts clearly recognizable with labeling, etc. for the prevention of the effects. Additionally, it is effective to keep the mode in repetitive magnetic field as much as possible since the effect increases in intermittent magnetic field mode.

Note: Wireless card (non-contact IC card) systems covered by this guideline consist of a remote reader (reader/writer) and IC card which transmits/receives data using low-intensity electromagnetic waves emitted from the reader, and the systems are used in transportation facilities, access controls, etc.

3 Guidelines for preventing the effects of electromagnetic waves from electronic article surveillance (EAS) devices on implantable medical devices (note)

A Any person with an implantable medical device should pass straight through the center of the passage without pausing around the area where EAS devices are installed and where EAS stickers (figure below) are attached.

B Any person with an implantable medical device should not stay around the EAS devices or lean on

these devices.

C Any person with an implantable medical device should immediately consult his/her physician if he/she feels any change in the physical condition.

D Relevant organizations should conduct further safety investigations in order to reduce the effects of EAS devices on implantable medical devices.

Figure. EAS sticker

Note: EAS devices covered by this guideline refer to devices designed to prevent shoplifting by sounding an alarm when goods attached with the sensor labels or tags pass through a corresponding sensor without being paid at the cash register.

* Permission to use the EAS sticker in the above Figure was obtained from the Japan Association of Electronic Article Surveillance Machines.

4 Guidelines for preventing the effects of electromagnetic waves from RFID devices (reader of electronic tags) on implantable medical devices (note 1)

(1) Gate type RFID devices (note 2)

A Any person with an implantable medical device should pass straight through the center of the passage without pausing around the area where gate-type RFID devices are installed and where RFID stickers (figure 1) are attached.

B Any person with an implantable medical device should not stay around the gate-type RFID devices or lean on these devices.

C Any person with an implantable medical device should immediately consult his/her physician if he/she feels any change in the physical condition.

D Relevant organizations should conduct further safety investigations in order to reduce the effects of gate-type RFID devices on implantable medical devices.

(2) Fixed-type RFID devices [note 2] (Limited to high output passive tag systems in the 950 MHz band [note 3]. This applies A to C below.)

A Any person with an implantable medical device should not come close within a radius of 1 meter from the area where fixed-type RFID devices are installed and where RFID stickers (combination of Figures 1 and 2) are attached.

B Any person with implantable medical device should immediately consult his/her physician if he/she feels any change in the physical condition.

C Relevant organizations should conduct further safety investigations in order to reduce the effects of fixed-type RFID devices on implantable medical devices.

(3) Hand-held type, fixed type (Excluding high output passive tag systems in the 950 MHz band. This applies A to C below.), and module type RFID devices [note 2]

A Any person who operates a hand-held type RFID device should keep the antenna region of the device approximately at least 22 cm away from the area where the implantable medical device is implanted.

B Any person with an implantable medical device should keep the antenna region of a fixed or module type RFID device approximately at least 22 cm away from the area where the device is implemented.

C Relevant organizations should conduct further safety investigations in order to reduce the effects of hand-held type, fixed-type and module type RFID devices on implantable medical devices.

For gate type RFID devices

For other types of RFID device

Figure 1. RFID stickers

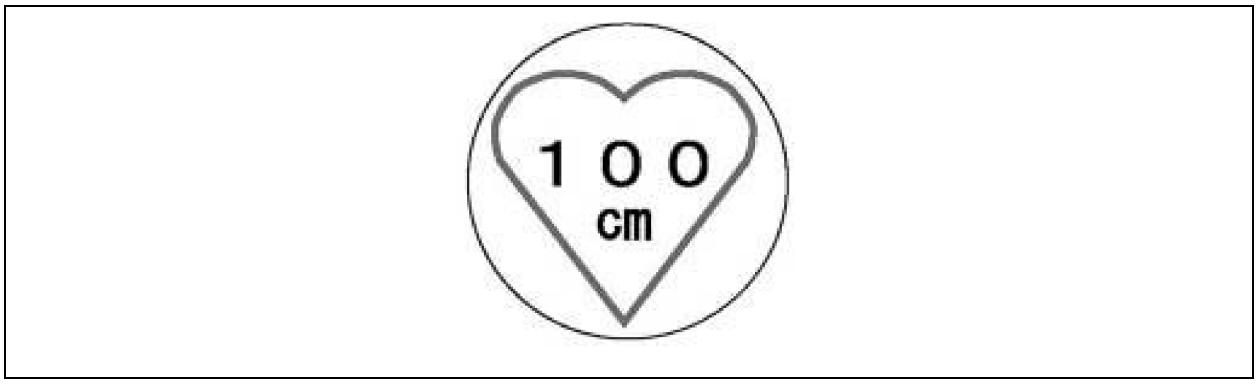

Figure 2. Sticker for fixed-type RFID devices (high output passive tag systems in the 950 MHz band)

Note 1: RFID devices covered here are those used in general environments such as in public facilities and/or business districts. RFID devices (dedicated RFID devices for controlled areas) used in the controlled areas inaccessible by the general public such as inside factory are excluded. In addition, in order to prevent the removal of dedicated RFID devices from controlled areas to general environments, it is prescribed by JAISA that precautions should be included in the user manual etc. and that a special sticker indicating "dedicated RFID for controlled areas" be attached (figure 3).

Figure 3. Special sticker for the dedicated RFID devices for controlled areas

Note 2: RFID devices are categorized as follows based on reader/writer configuration:
Gate type: the reader/writer is established in a gate configuration
Hand-held type: the reader/writer is a hand-held device that can be carried around
Fixed type: the reader/writer is used in a stationary condition
Module type: the reader/writer is built into a printer etc.

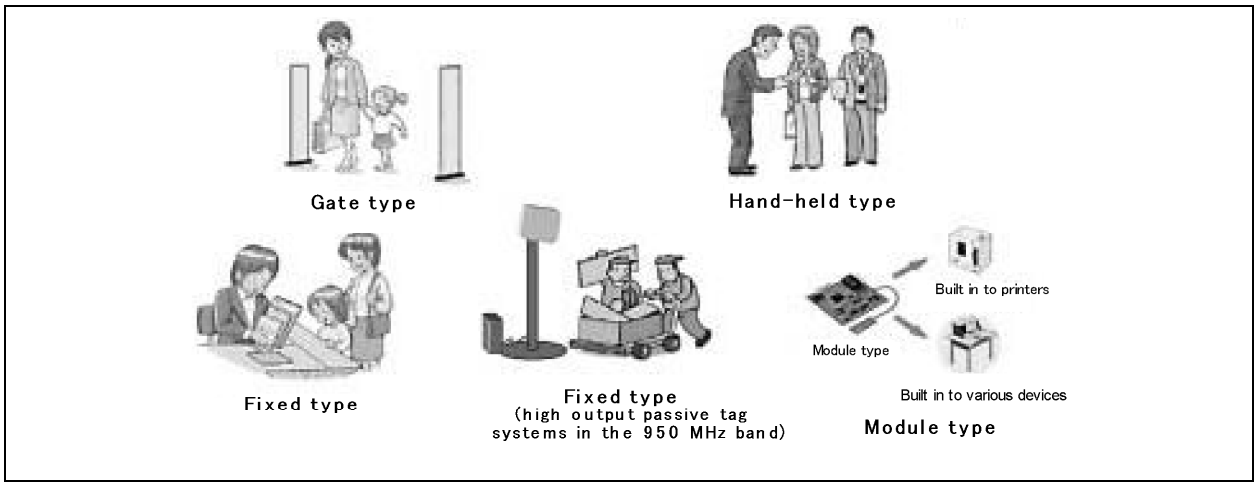

Figure 4. Types of RFID devices

Note 3: RFID devices that use frequencies (950 MHz) in the UHF band that enable comparatively long distance communications. For example, such system is expected to be used in applications such as for reading all of the attached tags in a container or on a pallet at one time.

* Permission to use the stickers in Figures 1 and 3 was obtained from the Japan Automatic Identification Systems Association.
Additionally, stickers for fixed-type RFID devices (high output passive tag systems in the 950 MHz band) in Figure 2 are posted with the permission of the Pacemaker Committee.

5 Measures for preventing the effects of electromagnetic waves from wireless LAN devices on implantable medical devices

Since only 1 model of the implantable medical device was affected by wireless LAN devices, all the users of this particular model have been alerted based on the investigation results through medical institutions with the cooperation of Ministry of Health, Labour and Welfare.

Therefore, any person with implantable medical device who has not been notified at this point does not require special attention to wireless LAN devices.

2

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 April 19 and 27, 2007.

1 Gadodiamide Hydrate

Brand Name (name of company)	Omniscan, Omniscan Syringe (Daiich-Sankyo Co., Ltd.)
Therapeutic Category	Intracorporeal diagnostic agents-Miscellaneous
Indications	The following imaging by magnetic resonance imaging (MRI) • Cerebrospinal imaging • Imaging of the trunk/limbs

<<**PRECAUTIONS** (underlined parts are additions)>>

[Relative Contraindications]

Patients with serious renal disorder (Nephrogenic systemic fibrosis may occur. The drug is essentially cleared through the kidney. If this product is administered to patients with decreased kidney function, worsening of conditions including renal failure acute etc. may occur due to delayed excretion.)

[Adverse Reactions (clinically significant adverse reactions)]

Nephrogenic systemic fibrosis (NSF): Nephrogenic systemic fibrosis may occur in patients with serious renal disorders. Patient should be carefully monitored for the emergence of itchiness of the skin, swelling, sclerema, joint stiffness, muscle weakness etc. following administration.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2004 to March 31, 2007) (events for which a causality to the drug could not be denied)

- Nephrogenic systemic fibrosis (NSF): 1 case (no fatal case)

The number of patients treated with Gadodiamide for a year estimated by MAH (Marketing Authorisation Holder): approximately 500000 (April 2006 to March 2007)

Marketed in Japan in: June 1996

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 20s	MRI test (Chronic renal failure, post operative schwannoma in the spinal lumbar canal, epilepsy, hepatitis C, papillary thyroid cancer, atrial fibrillation, and encapsulating peritoneal sclerosis)	10 mL Once	**Nephrogenic systemic fibrosis (NSF)** The patient was treated with peritoneal dialysis (PD). His thyroid function was normal. PCR persisted negative for Hepatitis C virus was confirmed. On day 1 of administration: 10 mL of this drug was intravenously administered. 6 days after administration: Redness, itching, and wheals occurred around forearm. 17 days after administration: The redness, itching, and wheals extended to lower thigh, later, significant sclerosis in the extremities progressed. PD was switched to haemodialysis for encapsulating peritoneal sclerosis. Approximately 30 days after administration: Limited joint range of motion and difficulty in walking occurred. 49 days after administration: Alprostadil alfadex ointment was started to apply. 63 days after administration: Methylprednisolone pulse therapy (500 mg/day) was conducted for encapsulating peritoneal sclerosis (until 65 days after administration). 66 days after administration: Dosage of prednisolone was increased from 40 mg to 60 mg/day for encapsulating peritoneal sclerosis. Although partial improvement in the cutaneous findings on the upper extremities was observed, limited joint range of motion in the lower extremities and difficulty in walking persisted. Surface of the skin was hardened like wood-grain and became crusted (although dimensions were somewhat diminished, 2/3 – 3/4 still persisted). The patient intermittently complained of severe pain on the skin.
	Concomitant medications: lisinopril, clonazepam, pancol/B_2/B_6/nicotinamide, alfacalcidol, amlodipine besilate, ferrous sulfate, prednisolone, famotidine.			

Clinical Laboratory Values

	On day 1 of administration	6 days after administration	13 days after administration	73 days after administration
Serum creatinine (mg/dL)	9.8	10.1	10.3	6.4
BUN (mg/dL)	79	100	95	37
WBC (/mm^3)	16610	16170	9670	28560
RBC ($\times10^4$/mm^3)	423	403	354	241
Platelet count ($\times10^4$/mm^3)	32	18.6	14.3	10.9
AST (GOT) (IU/L)	11	5	15	15
ALT (GPT) (IU/L)	51	24	85	24
γ-GTP (IU/L)	25	--	--	--
Total bilirubin (mg/dL)	0.4	--	--	--
CRP (mg/dL)	0.1	0.3	0.1	0.6

BUN: Blood Urea Nitrogen
WBC: White Blood Cell
RBC: Red Blood Cell
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
γ-GTP: γ-Glutamyltranspeptidase
CRP: C-Reactive Protein

2 Cabergoline

Brand Name (name of company)	Cabaser Tab. 0.25 mg and 1.0 mg (Pfizer Japan Inc.)
Therapeutic Category	Antiparkinsonian agents
Indications	Parkinson's disease Galactorrhoea Hyperprolactinaemic disorders of ovulation Hhyperprolactinemic disorders due to pituitary adenomas (limited to cases not requiring surgical procedure) Postpartum lactation inhibition

<<**PRECAUTIONS** (underlined parts are additions)>>

[Contraindications]

Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases [Symptoms may be worsened (See "Important Precautions" section)].

[PRECAUTIONS of Indications]

Administration of this drug should be limited to patients with insufficient treatment efficacy or limitations of tolerability with non-ergot preparations for the treatment of Parkinson's disease. (See "Important Precautions" and "Adverse Reactions" sections)

[Important Precautions]

Compared to non-ergot preparations, there have been more frequent reports of cardiac valvulopathy and fibrosis occurring during the administration of ergot preparations including this drug. Administration of this drug should be initiated under supervision of a physician with sufficient knowledge and experience in the pharmacotherapy of Parkinson's disease. Physicians must evaluate the risk and benefit balance of using this drug during the administration (See "Adverse Reactions" section). Cardiac valvulopathy may occur with a long-term administration of this drug. Patients should be carefully monitored by the following tests prior to/during administration. Additionally, there have been reported cases of improvement by discontinuation of the drug.

1) Before starting administration of this drug, check for the presence/absence of potential cardiac valvulopathy through physical examinations such as auscultation and echocardiography etc.
2) During administration of this drug, echocardiography should be conducted within 3 to 6 months after initiation of administration and at least every 6 to 12 months thereafter. Administration of this drug should be discontinued if cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis were confirmed by echocardiography etc. Patients should be carefully monitored through periodic observation (physical examinations such as auscultation, chest X-ray, and CT etc.) (See "Adverse Reactions" section).

Interstitial pneumonia, pleurisy, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, and retroperitoneal fibrosis may occur. Patients should be carefully monitored. Patients should be instructed to discontinue administration and to contact a physician immediately if pyrexia, cough, chest pain, shortness of breath, and dyspnoea etc. occur (See "Adverse Reactions" section).

[Adverse Reactions (clinically significant adverse reactions)]

Pleurisy, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion: Pleurisy, pleural effusion, pericardial effusion may occur. When this drug is administered to patients previously treated with this drug over the long term or an ergot preparation possessing dopamine receptor stimulating action, pleural fibrosis, pulmonary fibrosis, and pericarditis may occur. If chest pain, oedema, respiratory symptoms etc. occur during the administration of this drug, chest X-ray examination should be performed immediately. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Cardiac valvulopathy: Patients should be carefully monitored through periodic observation (physical examinations such as auscultation, chest X-ray, and CT etc.) If there is onset or aggravation of cardiac murmur, chest X-ray, and echocardiography tests etc. should be conducted immediately. If cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis are observed, administration should be discontinued and appropriate measures should be taken.

Retroperitoneal fibrosis: Cases of retroperitoneal fibrosis have been reported. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2004 to March 31, 2007) (events for which a causality to the drug could not be denied)

- Pleurisy: 2 cases (no fatal case)
- Pericardial effusion: 1 case (no fatal case)
- Cardiac valvulopathy: 7 cases (no fatal case)
- Retroperitoneal fibrosis: 1 case (no fatal case)

The number of patients treated with Cabergoline for a year estimated by MAH: approximately 70000 (2006)

Marketed in Japan in: August 1999

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Parkinson's disease (hypertension and cholelithiasis)	2 mg 910 days	**Pleurisy** Medical history: malignant neoplasm of tongue and gastric cancer On day 1 of administration: Administration of this drug was started for Parkinson's disease. Approximately on day 780 of administration: Chest pain in the left side manifested. On day 786 of administration: Pleural effusion in the left side was confirmed in the chest X-ray. Pleural puncture was conducted. Effusion pleural bloody was confirmed by appearance, specific gravity, rivalta, cell count, LDH, protein**,** glucose, and adenosine deaminase were 1.030, (+), 2500, 499 IU/L, 4.2 g/dL, 74.4 mg/dL, and 33.1 IU/L, respectively. On day 793 of administration: Pleural effusion drainage was conducted. No malignant cells were observed in the pleural effusion from on days 786 and 793 of administrations, and an increase in eosinophils was confirmed. Gram stain was negative. Effusion pleural bloody was confirmed by appearance, specific gravity, rivalta, cell count, LDH, protein**,** glucose, and adenosine deaminase were 1.025, (+), 1825, 687 IU/L, 3.5 g/dL, 69.2 mg/dL, and 27.2 IU/L, respectively. On day 910 of administration (day of discontinuation): Pleural effusion drainage was conducted again (LDH, protein, and glucose were 261 IU/L, 3.1 g/dL, and 80.9 mg/dL, respectively). The patient experienced shortness of breath and breathing difficulty. Administration of this drug was discontinued as pleurisy due to this drug was suspected. 27 days after discontinuation: CT (lungs) confirmed decreasing tendency in the pleural effusion. Chest pain was disappeared. Breathing difficulty and shortness of breath were improved. 42 days after discontinuation: Pleural effusion drainage was considered no longer necessary as CT and X-ray plain films confirmed decreasing tendency in the pleural effusion as well as alleviation of the subjective symptoms.
	Concomitant medications: selegiline hydrochloride, levodopa/carbidopa, ursodeoxycholic acid, atenolol, amlodipine besilate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 70s	Parkinson's disease (constipation)	0.25 mg 7 days ↓ 0.5 mg 21 days ↓ 1 mg 14 days ↓ 2 mg 82 days	**Pericardial effusion** Medical history: cholelithiasis and cholecystectomy On day 1 of administration: Administration of this drug at 0.25 mg was started. On day 8 of administration: The dose of this drug was increased to 0.5 mg. On day 29 of administration: The dose of this drug was increased to 1 mg. On day 43 of administration: The dose of this drug was increased to 2 mg. On day 115 of administration: Exertional shortness of breath and bilateral pleural effusion were confirmed. On day 125 of administration (day of discontinuation): The patient was hospitalized for complete medical examination of the cause. Administration of this drug was discontinued for a suspected adverse reaction. 1 day after discontinuation: Although echocardiography confirmed pericardial fluid, cardiac function was almost normal. 9 days after discontinuation: No abnormalities were confirmed at auscultation. Bilateral pleural effusion was confirmed by CT. Mild exertional dyspnea was confirmed. 17 days after discontinuation: Chest X-ray confirmed bilateral pleural effusion. Administration of diuretics (spironolactone at 50 mg/day) was started as volume of pleural effusion was unchanged. 23 days after discontinuation: CT confirmed slight decrease in pleural effusion. Pericardial fluid was also decreased. 24 days after discontinuation: The patient was recovering. 26 days after discontinuation: The patient was discharged from the hospital.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female 60s	Parkinson's disease (sleep apnoea syndrome and hypercholesterolaemia)	4 mg 1554 days	**Cardiac valvulopathy (suspected)** 1386 days before administration: No findings were suggesting cardiac valvulopathy in echocardiography. On day 1 of administration: Administration of this drug was started at 4 mg. On day 1386 of administration: Blood pressure was 169/87 mmHg (higher value than in the past). On day 1464 of administration: Shortness of breath manifested. Cardiac murmur was confirmed at auscultation. On day 1522 of administration: Function in the left ventricle was normal. Ventricular wall motion was normal, too. Mild tricuspid regurgitation was noted. Right ventricle systolic pressure was almost equal to 35 mmHg. Considering the mild tricuspid regurgitation, systolic pulmonary artery pressure was slightly increased. On day 1527 of administration: The result of echocardiography revealed aortic valve insufficiency. Tapering of this drug was started. On day 1549 of administration: Two-dimensional, M-mode and Doppler echocardiograms were conducted. Decreased wall motion from left ventricular wall through septal ventricular wall without decrease in the thickness of myocardial wall was confirmed. Ejection fraction (referential value: 58%–89%): 55% and 46% Aortic regurgitation: moderate, mitral regurgitation: mild, tricuspid regurgitation: mild, right ventricular systolic pressure was 31 mmHg, pulmonary valve regurgitation: stage I Calcification in tricuspid valve, right coronary cusp, and noncoronary cusp were confirmed. Tricuspid regurgitation of 0.48 cm regurgitant jet width was confirmed. Finding of decreased cardiac wall motion was confirmed from front side of left ventricle through septal ventricular wall. On day 1554 of administration: (day of discontinuation) Aortic valve incompetence was confirmed by the result of reexamination by echocardiography. Administration of this drug was discontinued.
	Concomitant medications: levodopa/benserazide hydrochloride, amantadine hydrochloride, selegiline hydrochloride, atorvastatin calcium hydrate, pergolide mesilate			

3 Pergolide Mesilate

Brand Name (name of company)	Permax Tablets 50 μg and 250 μg (Eli Lilly Japan K.K.) Veceral Tablets 50 μg and 250 μg (Taiyo Yakuhin Co., Ltd.) Pergolide Tablets 50 μg and 250 μg "SAWAI" (Medisa Shinyaku Inc.) Pergolin Gran. 0.025% (Daito Pharmaceutical Co., Ltd.) Pergolide Mesilate Tablets 50 μg and 250 μg "AMEL" (Kyowa Pharmaceutical Industry Co., Ltd.) Pergolide Mesilate Tablets 50 μg and 250 μg "Merck" (Merck & Co., Inc.)
Therapeutic Category	Antiparkinsonian agents
Indications	Parkinson's disease

<<**PRECAUTIONS** (underlined parts are additions)>>

[Contraindications]

Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases [Symptoms may be worsened (See "Important Precautions" section)].

[PRECAUTIONS of Indications]

Administration of this drug should be limited to patients with insufficient treatment efficacy or limitations of tolerability with non-ergot preparations (See "Important Precautions" and "Adverse Reactions" sections).

[Important Precautions]

Compared to non-ergot preparations, there have been more frequent reports of cardiac valvulopathy and fibrosis occurring during the administration of ergot preparations including this drug. Administration of this drug should be initiated under supervision of a physician with sufficient knowledge and experience in the pharmacotherapy of Parkinson's disease. Physicians must evaluate the risk and benefit balance of using this drug during the administration (See "Adverse Reactions" section).

Cardiac valvulopathy may occur with a long-term administration of this drug. Patients should be carefully monitored by the following tests prior to/during administration. Additionally, there have been reported cases of improvement by discontinuation of the drug.

1) Before starting administration of this drug, check for the presence/absence of potential cardiac valvulopathy through physical examinations such as auscultation and echocardiography etc.
2) During administration of this drug, echocardiography should be conducted within 3 to 6 months after initiation of administration and at least every 6 to 12 months thereafter. Administration of this drug should be discontinued if cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis were confirmed by echocardiography etc. Patients should be carefully monitored through periodic observation (physical examinations such as auscultation, chest X-ray, and CT etc.) (See "Adverse Reactions" section).

Fibrosis may occur. Patients should be carefully monitored (physical examinations, X-ray, echocardiography, CT scan etc.) as necessary during the administration of this drug (See "Adverse Reactions" section).

[Adverse Reactions (clinically significant adverse reactions)]

Cardiac valvulopathy: Patients should be carefully monitored through periodic observation (physical examinations such as auscultation, chest X-ray, and CT etc.) If there is onset or aggravation of cardiac murmur, chest X-ray, and echocardiography tests etc. should be conducted immediately. If cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2004 to March 31, 2007) (events for which a causality to the drug could not be denied)

- Cardiac valvulopathy: 4 cases (no fatal case)

The number of patients treated with Pergolide Mesilate for a year estimated by MAH: approximately 30000 (2006)

Marketed in Japan in: August 1994

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Parkinson's disease (mild) (hypertension, hyperlipidemia)	250 μg Approx. 1 month ↓ 1000 μg Approx. 6 months ↓ 750 μg Approx. 15 months ↓ 1000 μg Approx. 1 month ↓ 1250 μg Approx. 3 months ↓ 1000 μg Approx. 5 months ↓ 750 μg Approx. 1 month ↓ 450 μg 3 days ↓ 300 μg 3 days ↓ 150 μg 3 days ↓ 100 μg 3 days	**Cardiac valve disease** 4 years before administration: Parkinson's syndrome was developed. On day 1 of administration: Administration of this drug was started at 250 μg. (It had been administered at 250–1250 μg/day.) Approx.1 year after administration: Cabergoline at 1 mg/day was added. Later dosage was increased to 4 mg/day. Approx. 2 years after administration: The patient noted palpitations during administration of this drug at 1250 μg. Approx. 2 years and 2 months after administration: Dyspnoea manifested. The dosage of this drug was reduced to 1000 μg. Approx. 2 years and 5 months after administration: Aggravation of dyspnoea occurred. The patient was hospitalized for cardiac failure. Atrial fibrillation was confirmed. Echocardiography confirmed mild mitral regurgitation but not tricuspid regurgitation. Approx. 2 years and 6 months after administration: Conditions were improved. The patient was discharged from the hospital. As he noted palpitations and loss of consciousness occurred, the patient was hospitalization for complete medical examination. Approx. 2 years and 7 months after administration: The dosage of this drug was reduced to 750 μg. Approx. 2 years and 8 months after administration: The patient was discharged from the hospital. Body weight (BW) at discharge was 73 kg. Increased BW (75 kg) was confirmed on outpatient visit and the dosage of furosemide was increased. 3 days later (follow-up day), BW became 76 kg and oedema lower limb manifested. X-ray confirmed pleural effusion in the right side. The patient was readmitted to the hospital for cardiac failure. Urination was insufficient in spite of increased diuretic and echocardiogram was conducted upon hospitalization. Although left ventricular end-diastolic diameter was approximately 50 mm, strong mitral regurgitation and restriction in posterior mitral leaflet movement were observed.

				Dysfunction of chordae tendinea was considered from the echo images. Tapering dosage of this drug was conducted. Approx. 2 years and 9 months after administration: (day of discontinuation) Administration of this drug and cabergoline was discontinued. Transesophageal echocardiogram suggested a slight improvement tendency in mitral valve restriction. However, no clear improvement tendency was observed on later echocardiogram (transthoracic).
	Concomitant medications: cabergoline, levodopa/benserazide hydrochloride, amantadine hydrochloride, bromocriptine mesilate, selegiline hydrochloride, furosemide, metildigoxin, warfarin potassium, spironolactone, magnesium oxide			

4 Risperidone

Brand Name (name of company)	Risperdal Fine Granules 1%, Risperdal Tablets 1 mg, 2 mg, and 3 mg, Risperdal Oral Solution 1 mg/mL (Janssen Pharmaceutical K. K.)
Therapeutic Category	Psychotropics
Indications	Schizophrenia

<<**PRECAUTIONS** (underlined parts are additions)>>

[Important Precautions]

Aggravation of hyperglycaemia or diabetes mellitus leading to diabetic ketoacidosis and diabetic coma may occur with administration of this drug. Caution should be exercised for the onset of symptoms such as thirst, excessive drinking, polyuria, and pollakiuria etc. Especially, patients with diabetes mellitus, a history of diabetes mellitus, or risk factors for diabetes mellitus should be carefully monitored through measuring blood glucose levels etc.

Patients and their family members should be fully advised of the possible occurrence of these adverse reactions and be instructed to be alerted to abnormalities such as thirst, excessive drinking, polyuria, and pollakiuria, and to immediately discontinue administration and receive a consultation from a physician if such symptoms occur.

[Adverse Reactions (clinically significant adverse reactions)]

Hyperglycaemia, diabetic ketoacidosis, diabetic coma: Aggravation of hyperglycaemia or diabetes mellitus leading to diabetic ketoacidosis and diabetic coma may occur. Caution should be exercised for onset of symptoms such as thirst, excessive drinking, polyuria, and pollakiuria etc. Patients should be carefully monitored through measuring blood glucose levels etc. If any abnormalities are observed, administration should be discontinued and appropriate measures such as administration of insulin product etc. should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2004 to March 8, 2007) (events for which a causality to the drug could not be denied)

- Diabetic ketoacidosis: 3 cases (of which 1 had a fatal case)

The number of patients treated with Risperidone for a year estimated by MAH: approximately 417000 (2006)

Marketed in Japan in: June 1996

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Schizophrenia (diabetes mellitus and Basedow's disease)	3 mg 127 days	**Diabetic ketoacidosis** Approx. 1 year before administration: The patient was receiving treatment with levomepromazine maleate and tiapride hydrochloride. There were thirst and excessive drinking of coke and coffee etc. at approximately 1.5 L/day around the same time. Postprandial blood glucose levels were 90–130 mg/dL on outpatient visits of once every 3 months. Glucose tolerance impaired was not suggested. The patient had a family history of a sister with diabetes mellitus and Basedow's disease. On day 1 of administration: Tiapride hydrochloride was switched to this drug for complaint of hallucination, auditory and persecutory delusion. On day 85 of administration: Postprandial blood glucose level and sugar urinary were 293 mg/dL and (2+), respectively. Hyperglycaemia was suggested for the first time. On day 127 of administration: (day of discontinuation) Appetite impaired developed. Administration of all drugs was discontinued. 3 days after discontinuation: The patient became almost bedridden. 5 days after discontinuation: The patient became unresponsive to calling, and was sent to the ER. The patient was hospitalized for coma, dehydration, and infectious disease (CPR 12.96 mg/dL) due to diabetic ketoacidosis with JCS 300, blood glucose 926 mg/dL, BGA (pH 7.14, AG 34 μg/mL, BE–24 mEq/L), and urine ketone (2+). The patient received treatment with insulin and fluid replacement etc. The patient was later diagnosed with type I DM (SPIDDM) with anti-GAD antibody 45500 and insulin of lower limit of normal. The patient was diagnosed with Basedow's disease as TSH receptor antibody was positive (30.4%.) Polyglandular autoimmune syndrome type III (PGA) was diagnosed from DM, Basedow's disease, and abdominal vitiligo. 1 month after discontinuation: The patient was instructed for insulin self-injection and was discharged from the hospital. She was recovered.
	Concomitant medications: levomepromazine maleate, trihexyphenidyl hydrochloride, biperiden hydrochloride, diazepam, Takadiastase/botanical products, magnesium oxide, protoporphyrin sodium			

Clinical Laboratory Values

	On day 1 of administration	On day 85 of administration	5 days after discontinuation
BG (mg/dL)	138	293	926

BG: Blood Glucose

3

Revision of PRECAUTIONS

(No. 187)

(1) Drugs

This section presents details of revisions to PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated April 27, 2007 (excluding those presented in "2. Important Safety Information" of this Bulletin).

1 <Antipyretics and analgesics, anti-inflammatory agents> Ampiroxicam

[Brand Name]	Flucam Capsules 13.5 mg and 27 mg (Pfizer Japan Inc.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with an increase in AST (GOT) and ALT (GPT) etc., and jaundice may occur. Patients should be carefully monitored through liver function test etc. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

2 <Antipyretics and analgesics, anti-inflammatory agents> Piroxicam (oral dosage form and suppository)

[Brand Name]	Baxo Capsules 10 and 20, Baxo Suppositories (Toyama Chemical Co., Ltd.), Feldene Suppositories (Pfizer Japan Inc.), and others
[Adverse Reactions (clinically significant adverse reactions)]	**Hepatic function disorder, jaundice:** Hepatic function disorder with an increase in AST (GOT) and ALT (GPT) etc., and jaundice may occur. Patients should be carefully monitored through liver function test etc. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

3 <Vasodilators> Nisoldipine (oral dosage form)

[Brand Name]	Baymycard Tablets 5 mg and 10 mg (Bayer Yakuhin, Ltd.), and others
[Contraindications]	Patients receiving miconazole
[Interactions (contraindications for concomitant use)]	Miconazole

<Bronchodilators>

4 Theophylline (extended release oral medication), (drug product with dosage and administration for pediatrics)

[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 Indications] **Asthmatic (asthmatoid) bronchitis:** It should be considered to prioritize other drug therapy since this indication is often accompanied by fever. (Many cases of convulsions during the administration of this drug have been reported in infants with fever.)

<Antineoplastics-Miscellaneous>

5 Oxaliplatin

[Brand Name] Elplat for Injection 100 mg (Yakult Honsha Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Acute renal failure:** Nephritis interstitial and tubular necrosis etc. leading to serious renal disorder such as acute renal failure etc. may occur. Patients should be carefully monitored. If renal function abnormalities (BUN, serum creatinine etc.) are observed, administration should be discontinued and appropriate measures should be taken.

<Antineoplastics-Miscellaneous>

6 Arsenic Trioxide

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

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

<Chemotherapeutics-Miscellaneous>

7 Miconazole

[Brand Name] Florid-F for Inj., Florid-F for LV. Infusion 0.267%, Florid Oral Gel (Mochida Pharmaceutical Co., Ltd.), and others

[Contraindications]

Patients receiving pimozide, quinidine, triazolam, simvastatin, azelnidipine, nisoldipine, ergotamine tartrate, and dihydroergotamine mesilate

[Interactions (contraindications for concomitant use)]

Azelnidipine and nisoldipine

<Anthelmintics>

8 Ivermectin

[Brand Name] Stromectol Tablets 3 mg (Banyu Pharmaceutical Co., Ltd.)

[Adverse Reactions (clinically significant adverse reactions)] **Toxic epidermal necrosis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome):** Toxic epidermal necrosis (Lyell syndrome), oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

(2) Medical devices

This section presents details of the revisions to PRECAUTIONS section of package inserts of medical devices that have been revised according to the Notification dated April 27, 2007.

1 Medical devices such as artificial lungs, blood pumps, and blood circuits etc. that consist of extra-corporeal circuit

[PRECAUTIONS]

When establishing/using extra-corporeal circuits with this medical device, refer to the most updated information such as the guidelines published by the academic society etc.

<References> The Japanese Society for Cardiovascular Surgery, the Japanese Association for Thoracic Surgery, the Japanese Society for Artificial Organs, the Japan Society of Extra-Corporeal Technology in Medicine, and the Japan Medical Devices Manufacturers Association: Guidelines for Standard Methods of Extra-Corporeal Circuit and its Safety Training

4

List of products subject to Early Post-marketing Phase Vigilance

(As of June 1, 2007)

Nonproprietary name / Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Itraconazole / Itrizole Injection 1%	Janssen Pharmaceutical K.K.	December 6, 2006
Ropinirole Hydrochloride / ReQuip Tablets 0.25 mg, 1 mg, and 2 mg	GlaxoSmithKline K.K.	December 6, 2006
Lansoprazole / Takepron Intravenous 30 mg	Takeda Pharmaceutical Company Limited	December 7, 2006
Losartan potassium/Hydrochlorothiazide / Preminent Tablets	Banyu Pharmaceutical Co., Ltd.	December 8, 2006
Polidocanol / Polidocasklerol 0.5% Inj. 2 mL, 1% Inj. 2 mL, and 3% Inj. 2 mL	Sakai Chemical Industry Co., Ltd.	December 14, 2006
Fexofenadine Hydrochloride / Allegra Tablets 30 mg	Sanofi-Aventis K.K.	January 9, 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 1mg[*3]	Astellas Pharma Inc.	January 26, 2007
Baclofen / Intrathecal Gabalon 0.005%, 0.05%, and 0.2%[*4]	Daiich-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 Parma Corporation	March 28, 2007
Valaciclovir Hydrochloride Valtrex Granules 50%*8	GlaxoSmithKline K.K.	April 18, 2007
Entacapone Comtan Tablets 100 mg	Novartis Pharma K.K.	April 19, 2007

*1: An 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: An additional indication for “the prevention of influenza A or B virus infection”
*3: An 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: An additional administration for “pediatrics”
*5: An additional indication for “the prevention of Aspergillosis and Candidiasis in hematopoietic stem cell transplant patients”
*6: An additional indication for “the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamo-pituitary disorders”
*7: An 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: An additional indication for “varicella”

Manuals for Management of Individual Serious Adverse Drug Reaction

The Manuals for Management of Individual Serious Adverse Drug Reactions have been presented in "Pharmaceuticals and Medical Devices Safety Information" No. 230 (November 2006 edition). The second series of the manuals including "drug-induced hypersensitivity syndrome" and "acute renal failure", and "thrombocytopenia" etc. have been finalized and are available at MHLW website (http://www.mhlw.go.jp/) and the pharmaceuticals and medical devices information website (http://www.info.pmda.go.jp/).

The manual names and common initial symptoms included in the Manuals for Management of Individual Serious Adverse Drug Reactions, presented above are shown in the **Table 1**, and the list of the manuals is shown in **Table 2**.

It is hoped that these manuals will be used by healthcare providers including physicians, dentists, and pharmacists as well as patients for achieving early recognition of and prompt response to serious adverse reactions.

Table 1 Manuals for Management of Individual Serious Adverse Drug Reactions released in June 2007

Manual name (adverse drug reaction)	Common initial symptoms
Drug-induced hypersensitivity syndrome	"Widely extended redness of skin", "Hyperthermia (38°C or higher)", "Sore throat", "Systemic malaise", "Decreased appetite", and "Swollen lymph nodes"
Acute renal failure	"Reduced urine volume", "Almost no urination", "Temporally increased urine volume", "Rash", "Oedema", and "Malaise"
Nephritis interstitial (tubulointerstitial nephritis)	"Pyrexia", "Rash", "Arthralgia", "Gastrointestinal symptoms such as feeling queasy, vomiting, diarrhoea, and abdominal pain", "Oedema", and "Reduced urine volume"
Thrombocytopenia	"Petechiae in the limbs", "Easily bruised", and "Easily bleeding (gingival bleeding/epistaxis/excessive menstrual bleeding)"
Thrombosis (thromboembolism, embolism, and infarction)	"Paralysis and numbness in the limbs", "Difficulty in speaking", "Chest pain", "Dyspnoea", and "Sudden unilateral pain and swelling in one side of the leg"
Bleeding tendency	"Petechiae in the limbs", "Easily bruised", "Epistaxis", "Gingival bleeding", "Stool discolored black (stool tarry)"
Disseminated intravascular coagulation (systemic hypercoagulative disorder and consumptive coagulopathy)	"Easily bruised", "Epistaxis", "Gingival bleeding", "Haematuria", "Bloody stool", "Eye (conjunctival) haemorrhage", "Consciousness disturbed", "Dyspnoea", "Palpitations", "Shortness of breath", "No urination", and "Jaundice"
Drug-induced anaemia (haemolytic anaemia, methaemoglobinaemia, aplasia pure red cell, sideroblastic anaemia, and anaemia megaloblastic)	"Poor complexion", "Fatigability", "Malaise", "Heaviness of head", "Palpitations", and "Shortness of breath"
Agranulocytosis (granulocytopenia and neutropenia)	"Sudden hyperthermia", "Chills", and "Sore throat"
Aplastic anaemia (pancytopenia)	"Easily bruised", "Oral and nasal mucosa haemorrhage", "Pyrexia", "Sore throat", "Pale skin and mucous membrane", "Fatigue", "Palpitations", "Shortness of breath", "Feeling poorly and dazed" and "Haematuria"

Table 2 Full list of the Manuals for Management of Individual Serious Adverse Drug Reactions (including those at drafting stage)

Field	Name of cooperating society	Subject adverse drug reaction
Dermatologicals	The Japanese Dermatological Association	○ Stevens-Johnson syndrome ○ Toxic epidermal necrosis ○ Drug-induced hypersensitivity syndrome Acute generalized exanthematous pustulosis
Hepatic	The Japan Society of Hepatology	Drug-induced hepatic disorder
Renal	The Japanese Society of Nephrology	○ Acute renal failure ○ Nephritis interstitial Nephrotic syndrome
Blood	The Japanese Society of Hematology	○ Aplastic anaemia ○ Bleeding tendency ○ Drug-induced anaemia ○ Agranulocytosis ○ Thrombocytopenia ○ Thrombosis ○ Disseminated intravascular coagulation Thrombotic thrombocytopenic purpura Heparin-induced thrombocytopenia
Respiratory system	The Japanese Respiratory Society	○ Interstitial pneumonia ○ Asthmatic attack due to nonsteroidal anti-inflammatory drug ○ Acute lung injury/Acute respiratory distress syndrome Pulmonary oedema Acute eosinophilic pneumonia Pulmonary alveolar haemorrhage
Alimentary tract	The Japanese Society of Gastroenterology	Ileus paralytic Peptic ulcer Pseudomembranous colitis Pancreatitis (acute pancreatitis)
Cardiovascular system	The Japanese Circulation Society	Ventricular tachycardia Cardiac failure congestive
Nervous and musculo-skeletal system	The Japanese Society of Neurology	○ Drug-induced parkinsonism ○ Rhabdomyolysis ○ Leukoencephalopathy Peripheral neuropathy Meningitis aseptic Acute disseminated encephalomyelitis Guillain-Barre syndrome Dyskinesia Convulsion/Epilepsy
Psychiatric	The Japanese Society of Clinical Neuropsychopharmacology	Neuroleptic malignant syndrome Depressive state
Metabolism and endocrine	The Japan Endocrine Society	○ Pseudoaldosteronism Thyrotoxicosis Hypothyroidism
	The Japan Diabetes Society	Hypoglycaemia Hyperglycaemia
Hypersensitivity	The Japanese Society of Allergology	Anaphylaxis Urticaria/Angioedema

Sensory organs (visual)	The Japanese Ophthalmological Society	Retinal disorder/Visual field defects Glaucomas
Oral cavity	The Japanese Society of Oral and Maxillofacial Surgeons	Drug-induced stomatitis
Bones	The Japanese Society of Oral and Maxillofacial Surgeons	Osteonecrosis of the jaw
	The Japanese Orthopaedic Association	Osteoporosis
Urinary organs	The Japanese Urological Association	Urinary retention (dysuria)

Note) Manuals marked with "○" are published.

Guidelines for Standard Methods of Extra-corporeal Circuit and Its Safety Training

The "Guidelines for Standard Methods of Extra-corporeal Circuit and Its Safety Training," which was in the process of being created as an operation to promote proper use of pharmaceuticals etc. in 2006, has been completed with the cooperation of the Japanese Society for Cardiovascular Surgery, the Japanese Association for Thoracic Surgery, the Japanese Society for Artificial Organs, the Japan Society of Extra-Corporeal Technology in Medicine, and the Japan Medical Devices Manufacturers Association and is presented in this section.

Standardized connection methods for extra-corporeal circuits (diagrams and check points for 3 types of circuit connections) used for the initial education are presented as a reference.

(
Figure 1. Connection model 1: Venous reservoir line
Figure 2. Connection model 2: Arterial reservoir line
Figure 3. Connection model 3: Line without reservoir
)

The full text of this guideline is posted on the website of MHLW (http://www.mhlw.go.jp/topics/2007/04/tp0427-10.html).

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Connection model 1: Venous reservoir line

⦿ Mandatory ○ Suggested

Venous line

⦿ Have measures to keep the venous line identifiable at the site of connection.
⦿ Have measures to monitor the sufficient oxygen supply to patient's tissues.
⦿ Have measures to monitor the in-circuit pressure when conducting blood drainage using assisted venous drainage.
○ Have measures that enable the expeditious replacement of circulating blood.

Pump line

⦿ Have measures to monitor the in-circuit pressure at the pump exit.

Arterial line

⦿ Have measures to keep the arterial line identifiable at the site of connection.
⦿ Have measures to remove bubbles and foreign substances.
⦿ Have measures to prevent back-flow in the purge line that is connected to the parts removing bubbles and foreign substances.
⦿ Have measures to monitor the in-circuit pressure of the arterial line.
○ Have measures to monitor the sufficient oxygen supply to patient's tissues.

Cardiotomy suction

⦿ Have measures to keep the cardiotomy suction identifiable at the site of connection.
⦿ Have measures to prevent back-flow when venting with the pump.

Gas line

⦿ Use sanitary tubes.
⦿ Have measures to keep the gas line identifiable at the site of connection.
○ Have measures to remove foreign substances in the gas line.

Accessory line

(1) Sampling line
⦿ Have measures to prevent back-flow into the arterial line.

Others

(1) Precautions
⦿ Prepare the recommendations of Joint committee of three academic society on vacuum assisted venous drainage (VAVD) when conducting blood drainage using the vacuum assisted line.
○ Have measures to remove the in-circuit foreign substances prior to implementing extra-corporeal circulation.

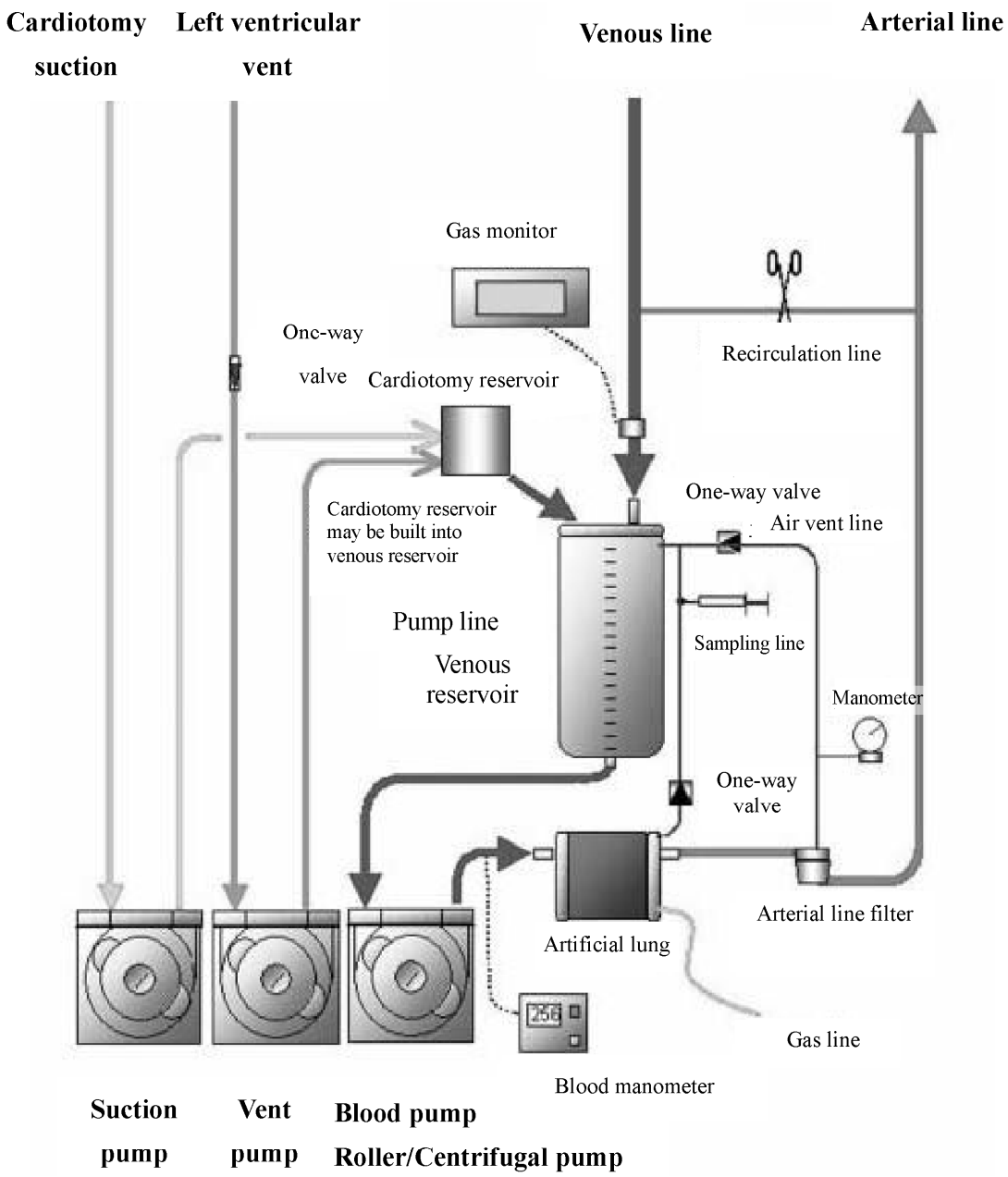

Figure 1. Connection model 1: Venous reservoir line

Connection model 2: Venous reservoir line

◉ Mandatory ○ Suggested

Venous line

◉ Have measures to keep the venous line identifiable at the site of connection.
◉ Have measures to monitor the sufficient oxygen supply to patient's tissues.
◉ Have measures to monitor the in-circuit pressure when conducting blood drainage using assisted venous drainage.
○ Have measures that enable the expeditious replacement of circulating blood.

Arterial line

◉ Have measures to keep the arterial line identifiable at the site of connection.
◉ Have measures to remove bubbles and foreign substances.
◉ Have measures to prevent back-flow in the purge line that is connected to the parts removing bubbles and foreign substances.
◉ Have measures to monitor the in-circuit pressure of the arterial line.
○ Have measures to monitor the sufficient oxygen supply to patient's tissues.

Cardiotomy suction

◉ Have measures to keep the cardiotomy suction identifiable at the site of connection.
◉ Have measures to prevent back-flow when venting with the pump.

Gas line

◉ Use sanitary tubes.
◉ Have measures to keep the gas line identifiable at the site of connection.
○ Have measures to remove foreign substances in the gas line.

Accessory line

(1) Sampling line
◉ Have measures to prevent back-flow into the arterial line.

Others

(1) Precautions
○ Have measures to remove the in-circuit foreign substances prior to implementing extra-corporeal circulation.

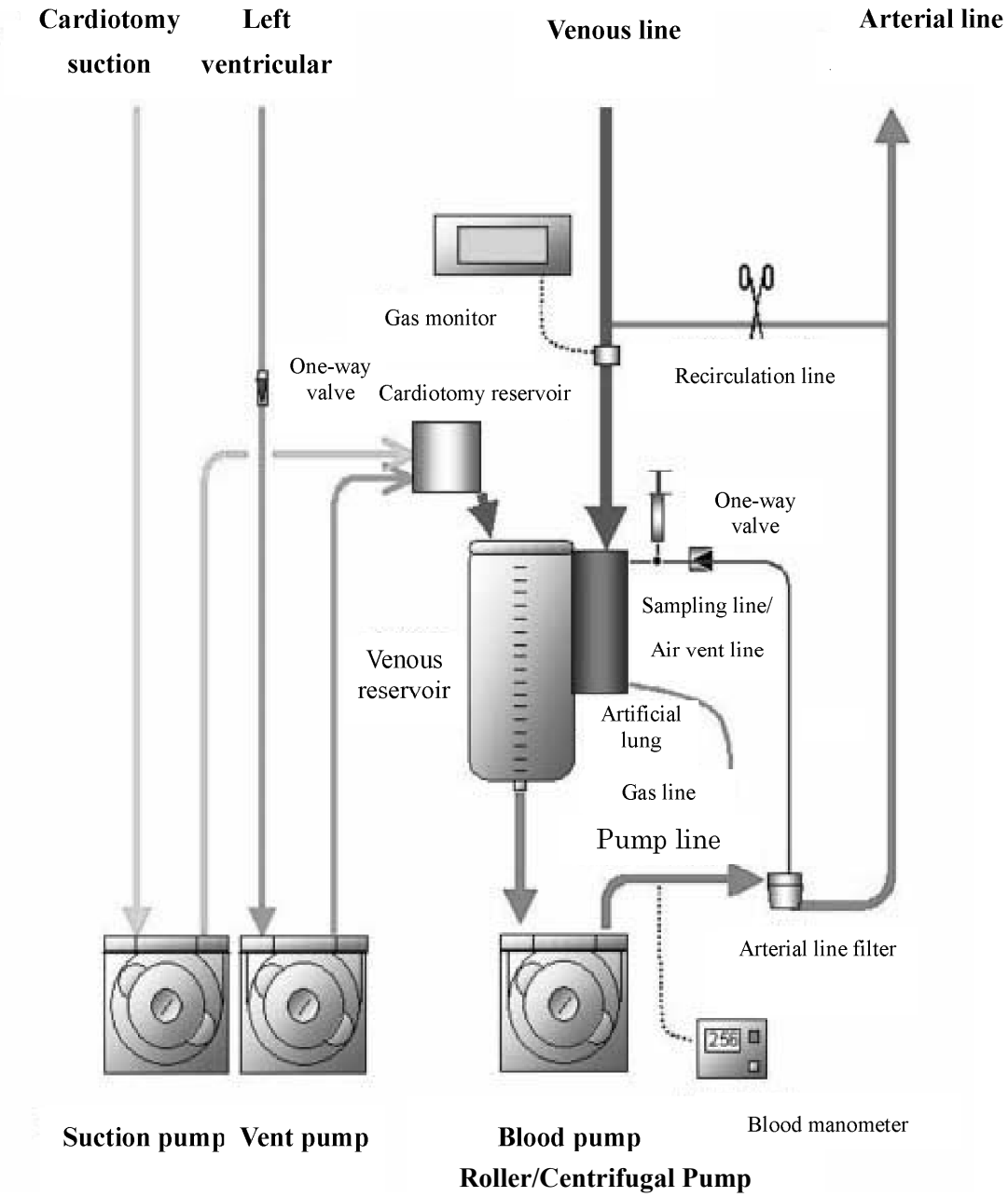

Figure 2. Connection model 2: Arterial reservoir line

Connection model 3: Line without reservoir

◉ Mandatory ○ Suggested

Venous line

◉ Have measures to keep the venous line identifiable at the site of connection.
◉ Have measures to monitor the sufficient oxygen supply to patient's tissues.
◉ Have measures to monitor the in-circuit pressure when conducting blood drainage using assisted venous drainage.
○ Have measures to remove the bubble and foreign substances when using the line without reservoir.
○ Have measures that enable the expeditious replacement of circulating blood.

Pump line

◉ Have measures to monitor the in-circuit pressure at the pump exit.

Arterial line

◉ Have measures to keep the arterial line identifiable at the site of connection.
○ Have measures to monitor the sufficient oxygen supply to patient's tissues.

Gas line

◉ Use sanitary tubes.
◉ Have measures to keep the gas line identifiable at the site of connection.
○ Have measures to remove foreign substances in the gas line.

Accessory line

(1) Sampling line
◉ Have measures to prevent back-flow into the arterial line.

Others

(1) Precautions
○ Have measures to remove the in-circuit foreign substances prior to implementing extra-corporeal circulation.

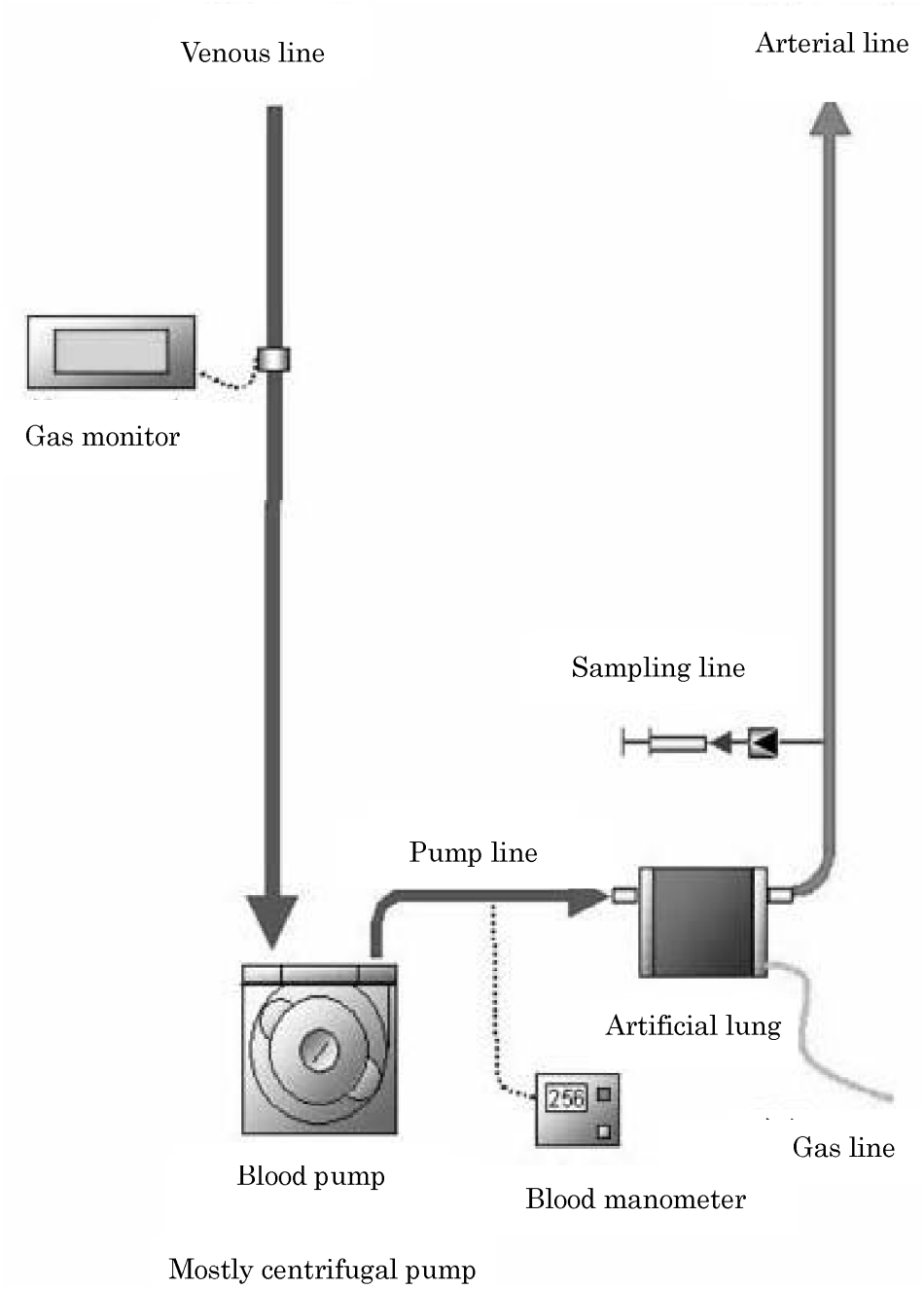

Figure 3. Connection model 3: Line without reservoir