

Pharmaceuticals and Medical Devices Safety Information

No. 235 April 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. 235 April 2007

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

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	Standardization of the number of drops for infusion sets and blood transfusion sets		Ministry of Health, Labour and Welfare (MHLW) is currently in the process of standardizing the specification of infusion sets, blood transfusion sets and infusion pumps, in relation to the number of drops per 1 mL. Two specifications i.e. 20 drops and 60 drops per 1 mL, have been established, and medical institutions etc. are being advised to consult the relevant manufacturers for the adjustment of flow rates of infusion pumps. The report introduces the background and the outline of changes etc.	3
2	Project of Japan Drug Information Institute in Pregnancy		In October 2005, Ministry of Health, Labour and Welfare (MHLW) established a “Japan Drug Information Institute in Pregnancy” within the National Center for Child Health and Development, for counseling and research activities. In view of the target area expanding to the whole country, as of April this year, the background and the outline of the project is introduced in this report.	6
3	Safety Information on the “Pharmaceuticals and Medical Devices Information Website” of the Pharmaceuticals and Medical Devices Agency		In order to promote safe use of pharmaceuticals and medical devices etc., a variety of safety information, including package inserts, are being provided on the pharmaceutical and medical devices information website. Notably, a wide range of information has been posted on the website since the establishment of the Pharmaceuticals and Medical Devices Agency in April 2004. This report introduces the background, and some of the main features.	10
4	Products subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of as of April 1, 2007.	13

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.

Standardization of the number of drops for infusion sets and blood transfusion sets

1. Introduction

Ministry of Health, Labour and Welfare (MHLW) is in the process of standardizing the specification of infusion sets and blood transfusion sets (hereafter referred to as “infusion sets etc.”) as well as infusion pumps, in relation to the number of drops per 1 mL. Two specifications i.e. 20 drops and 60 drops per 1 mL, have been established based on the MHLW Notification No. 112, March 25, 2005, “The List of Medical Devices designated by Minister of Health, Labour and Welfare in accordance with the Article 23-2-1 of the Pharmaceutical Affairs Law” for infusion sets etc., and on PFSB Notification No. 1124002 of Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW, November 24, 2005, on the “Establishment of approval standards for infusion pumps” in terms of infusion pumps. (Transition period is up to March 31, 2009)

In response, regarding response of medical institutions, HPB/GAD Notification No. 1124001 and PFSB/SD Notification No. 1124003, Director of General Affairs Division, Health Policy Bureau/ Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 24, 2005, on the “Response of medical institutions for establishment of approval standards for infusion pumps” has been issued advising medical institutions to consult the manufacturers of the relevant infusion pumps regarding the revision of the flow rate.

The report, therefore, aims to inform the background, outline of the changes etc. to the healthcare providers, in order to ensure medical safety.

2. Background

In accordance with the Article 23-2-1 of the Pharmaceutical Affairs Law, infusion sets etc. that are in conformity with the standards set by Minister of Health, Labour and Welfare, are certified and authorised for marketing. Until now, however, nationally uniform specification for infusion sets etc. did not exist regarding the number of drops per 1 mL. As a result, 4 types of infusion sets, with the number of drops of 15, 19, 20, 60 (for minidrip solution) per 1 mL, were being marketed. As for blood transfusion sets, 15 drops per 1 mL was the most popular type in use. Additionally, no standard has been established for the size of outlet port of infusion pumps according to the number of drops, and the size of outlet port of conventional infusion pumps has been configured to accommodate the use of infusion sets with the above described number of drops. This was not an ideal situation in terms of safety.

Therefore, uniform standards for the performance, quality and the purpose of use of infusion sets etc. were established by the MHLW Notification No. 112, March 25, 2005. As for the size of the outlet port, a standard was established as Japanese Industrial Standards (JIS) in consistent with the ISO Standards.

Furthermore, regarding the infusion pumps that are used with infusion sets with predetermined number of drops per 1 mL, PFSB Notification No. 1124002 of Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW, dated November 24, 2005, has been issued to establish the approval criteria for the infusion pumps. The criteria in relation to the standardization of the number of drops are indicated under the articles on specification and criteria, where it is mentioned that the use of infusion sets other than those with 20 drops/mL or 60 drops/mL is prohibited.

3. Outline of the changes

(1) Infusion sets etc.

(a) Devices subject to changes

- Infusion sets (dual-purpose infusion sets for the use with gravity feed/infusion pump, infusion sets for the use with infusion pump etc.)
- Blood transfusion sets (blood transfusion sets, blood transfusion sets for exchange blood transfusion)

(b) Details of the changes

Two specifications i.e. 20 drops and 60 drops (for minidrip), were established for infusion sets etc., as uniform standard regarding the number of drops per 1 mL did not exist until now.

(c) Transition Period

As the marketing of infusion sets that are used with 15 or 19 drops per 1 mL will be prohibited from April 1, 2009, the manufacturers will be making a shift from such infusion sets to 20 drops infusion sets etc., by March 31, 2009. 60 drop/mL infusion sets will be marketed without change.

Transition period

Current drop	Until March 31, 2009	After April 1, 2009
Standard type	15 drops	Standardized specification: 20drops
	19 drops	
	20 drops	
Precision type	60 drops	60 drops

(2) Infusion pump

(a) Devices subject to changes

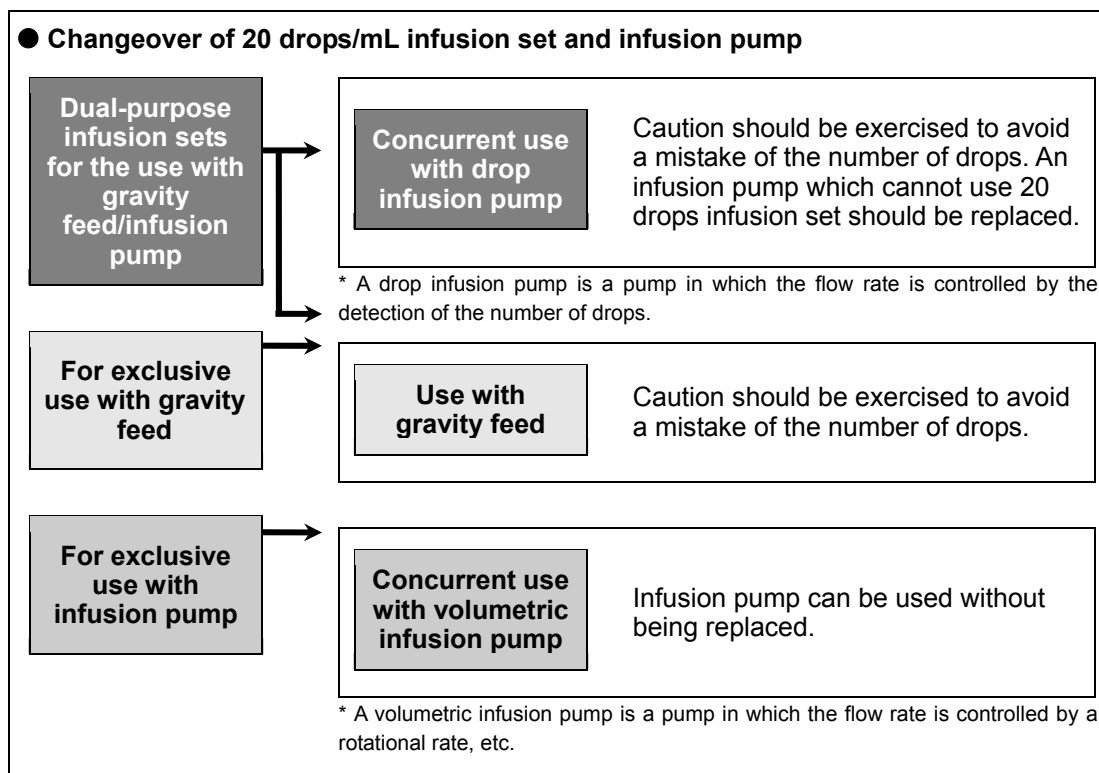
- Multi-purpose infusion pumps

(b) Details of the changes

Infusion pumps are categorized into 2 types, namely volumetric infusion pumps^{Note 1)} and drop infusion pumps^{Note 2)}, and standardization of the number of drops concerns the drop infusion pumps. Drop infusion pumps are used by setting the number of drops of infusion sets etc. prior to use. Therefore, when using a 20 drops infusion set, healthcare providers must check the package insert or instruction manual, or obtain the necessary information from the manufactures.

Note 1) A volumetric infusion is a system in which the operation of the fluid delivery mechanism that ensures an accurate volume output, is controlled at a fixed speed to achieve a constant flow rate.

Note 2) A drop infusion is a system in which the flow rate is controlled by the acceleration or deceleration of the fluid delivery mechanism, so that the flow rate detected by the drop sensor is made equal to the predetermined flow rate.



(c) Transition Period

Depending on the specification of the infusion pumps, some of them may not be used with 20 drops infusion sets. A changeover should be made to drop infusion pumps which can use 20 drops infusion sets, by March 31, 2009.

4. Request for healthcare providers

When using infusion sets etc. in medical institutions, the number of drops indicated on the packaging (e.g. nominal number of drops 1 mL ≈ 20 drops) should be confirmed, and caution should be exercised to avoid a mistake of the number of drops. Some infusion pumps have the function to cancel the number of drops set at 15 or 19, but others have not. Therefore, the specification of the infusion pump must be confirmed with the manufacturers, and pay attention to avoid setting mistakes, especially with the models which cannot cancel the setting. To confirm whether the infusion pump used in the medical institution is adapted to 20 drops, please consult the manufacturer of the infusion pump, indicating the model name and the manufacturing number.

It is hoped that that each medical institution is fully understood the standardization of the number of drops for infusion sets etc., and to ensure thorough care and attention when handling these devices.

5. Closing comments

The information on the standardization of the number of drops for infusion sets etc. can be obtained from the website of Japan Medical Devices Manufacturers Association (<http://www.jmed.jp/>) under the section on “the standardization of number of drops for infusion sets etc, and the color coding scheme for injection needles etc.”. For detailed information on the changes, please consult the manufacturers of the infusion sets etc. and infusion pumps that are used in each medical institution.

Moreover, similar information can also be obtained from the “Medical Safety Information” section on the Pharmaceutical and Medical Devices Information website of Pharmaceuticals and Medical Devices Agency (<http://www.info.pmda.go.jp/>).

Project of Japan Drug Information Institute in Pregnancy

1. Introduction

When using drugs during pregnancy, sufficient attention should be paid on their influence, not only on the mother but also on the fetus, especially with regard to the “teratogenicity” of the drug.

On the other hand, although very few drugs have actually been confirmed to have teratogenic effects on humans¹⁾, a tendency of excessive anxiety about drug-related risks has been reported²⁾, resulting in some cases where physicians etc. had withheld the necessary pharmacotherapy, or the patients had stopped taking the drugs by self-judgment, aggravating the health condition of the mother or causing adverse health effect on the fetus. Some patients even give up childbearing, because they are under medication for chronic diseases.

Given the difficulty in collecting accurate data on drug use during pregnancy, under present circumstances, a “Japan Drug Information Institute in Pregnancy” was established within the National Center for Child Health and Development on October 2005, to implement counseling and research activities in a limited area, on a trial basis. In view of the target area expanding to the whole country, the background and the outline of the project is presented in this report.

2. Background etc.

Ministry of Health, Labour and Welfare (MHLW) convened a “Conference on the collection of data regarding the administration of drugs etc. during pregnancy” on 3 occasions, January, July, and August 2005, with the committee members consisting not only of the specialist from the medical institutions providing counseling services on pregnancy and medicine, but also the experts on bioethics and the representatives from the general public. Discussions were held on various issues, including counseling methods, research methods on pregnancy outcome, informed consent for research etc. Based on the discussions of the conference, the “Japan Drug Information Institute in Pregnancy” was established within the National Center for Child Health and Development in October 2005, and the project started on a trial basis with its initial activities limited to Setagaya Ward, Tokyo. The target area for counseling was expanded to Tokyo and Kanagawa Prefecture by February 2006, to the Tokyo metropolitan area (7 prefectures, including Tokyo) from September 2006, and to the whole country with the cooperation of 5 institutions starting from this April.

3. Project of “Japan Drug Information Institute in Pregnancy”

(1) Content of operation

① Counseling

Counseling services, mainly through the attending physician or face-to-face counseling, are provided to pregnant women who are concerned about the influence of drug therapy on the fetus, or to women who wish to become pregnant.

Those seeking to receive counseling service, may use the “Japan Drug Information Institute in Pregnancy” by following the procedure below.

- a. If you wish to receive the counseling service, download the “Interview Sheet” and the

“Application Form for Counseling Service” from the website of “Japan Drug Information Institute in Pregnancy” (<http://www.ncchd.go.jp/kusuri/index.html>).

- b. The “Interview Sheet”, used to clarify the patient’s background information, must be completed by the patient in consultation with the attending physician. The “Application Form” shall be completed by the attending physician. A referral form issued by the attending physician may be substituted for “Application Form”.
- c. Send the “Interview Sheet” and the “Application Form for Counseling Service” to the “Japan Drug Information Institute in Pregnancy” by post.
- d. The “Japan Drug Information Institute in Pregnancy” will prepare explanatory documents for the physician.
- e. Based on these documents, the patient will receive explanations through one of the following 2 methods.
 - A physician/a pharmacist will directly provide counseling to the patient, at the out-patient department of the National Center for Child Health and Development or of the cooperating hospital.
 - A reply written by “Japan Drug Information Institute in Pregnancy” will be send to the attending physician, who will give the explanation to the patient.

If counseling service is to be provided at the out-patient department of the National Center for Child Health and Development, the specialized physician and the pharmacist of the “Japan Drug Information Institute in Pregnancy” who had prepared the documents will attend, so that counseling can be done paying due consideration to risk communication. In principle, this method is employed for counseling regarding drugs with high risk of teratogenicity, or for patients whose level of anxiety is high. It is also possible to receive counseling from specialized staff with knowledge, at the cooperating hospitals.

In the case of counseling by the attending physician, it will be possible to respond to the applications from distant locations or from pregnant women in the early stage of pregnancy who are feeling unwell and worried of traveling, because counseling will be done in the medical institutions near the patients.

② Survey of the infants

For the survey on the infants (pregnancy outcome survey), the National Center for Child Health and Development requests the patients at the time of application for counseling service, for their cooperation in supplying the post-delivery information.

As for the research method, the “Japan Drug Information Institute in Pregnancy” sends a postcard to the applicant 1 month after the expected date of birth, asking to return the card completed with the result of 1-month physical examination.

Moreover, in order for its purpose and the significance to be fully understood, the patients are explained during the counseling session that the information provided to them by the “Japan Drug Information Institute in Pregnancy” had been collected by the same method as the survey, and that returning the pregnancy outcome card will contribute to the women who will become pregnant in the future.

(2) Current situation

Since the establishment of the “Japan Drug Information Institute in Pregnancy”, there have been 111 consultation requests for FY2005, and 304 consultation requests for FY2006 up to February 2007. Initially, there were about some dozens of applications per month, but the number increased since September 2006 when the target area was expanded to the Tokyo Metropolitan area (7 prefectures, including Tokyo), and there are currently about 30 consultations per month.

As for the survey of the infants, the collection rate of the pregnancy outcome card is currently very high. The results of the collected cards will continue to be accumulated and analyzed in the future.

4. Future plans

In the future, the result of the pregnancy outcome survey will be consolidated into a database and evaluated, so that the safety information regarding the use of drugs in pregnant women can be disseminated by reflecting the acquired information in package inserts etc.

5. Request for healthcare providers

Healthcare providers are requested to be familiar with the pregnancy and medicine counseling service of the “Japan Drug Information Institute in Pregnancy”, and to make use of the service as necessary.

<References>

- 1) Schardein JL. Chemically induced birth defects, 3rd ED. NY:Marcel Dekker, Inc, 2000.
- 2) Koren G, Bologna M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. Am J Obstet Gynecol 1989;160 (5I):1190-4.

Figure. Japan Drug Information Institute in Pregnancy

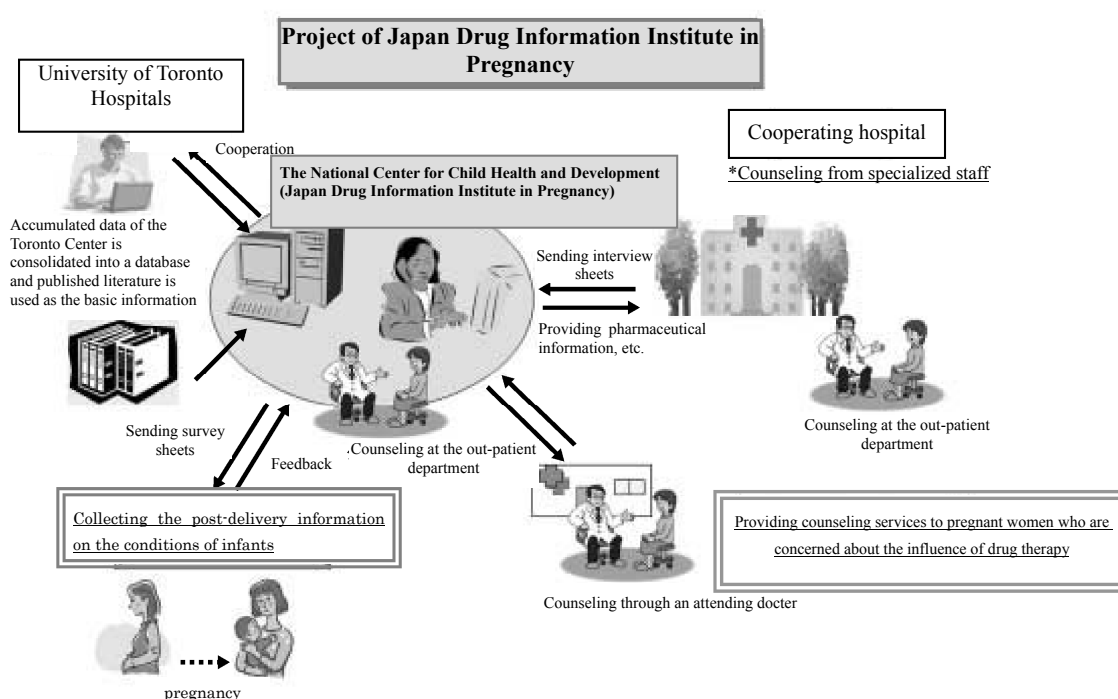


Table. List of cooperating hospitals

National Center for Child Health and Development

Address: 2-10-1 Okura, Setagaya-ku, Tokyo, 157-8535

TEL: 03-5494-7845 (main line)

FAX: 03-3415-0914

(Operating hours: 10:00 – 16:00 Monday to Friday, excluding holidays)

Website: <http://www.ncchd.go.jp/>

(cooperating hospital)

- National Hospital Organization Sendai Medical Center

Address: 2-8-8 Miyagino, Miyagino-ku, Sendai, Miyagi, 983-8520

TEL: 022-293-1171

(Operating hours: 10:00 – 16:00 Monday to Friday, excluding holidays)

- Tsukuba University Hospital

Address: 2-1-1 Amakubo, Tsukuba, Ibaraki, 305-8576

TEL: 029-853-3630

FAX: 029-853-7025

(Operating hours: 9:00 – 16:00 Monday to Friday, excluding holidays)

- Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital

Address: 2-2-2 Toranomon, Minato-ku, Tokyo, 105-8470

TEL: 03-3588-1111 (extension 3410)

FAX: 03-3505-1764

(Operating hours: 8:30 – 17:00 Monday to Friday, excluding holidays)

- St Luke's International Hospital

Address: 9-1 Akashi-cho, Chuo-ku, Tokyo, 104-8560

TEL: 03-5550-2412

FAX: 03-3541-1156

(Operating hours: 9:00 – 16:00 Monday to Friday, excluding holidays)

- Osaka Medical Center and Research Institute for Maternal and Child Health

Address: 840, Murodocho, Izumi-shi, Osaka, 594-1101

TEL: 0725-56-1220

(The above telephone number is planned to be available, starting from May 14, 2007)

Safety Information on the “Pharmaceuticals and Medical Devices Information Website” of the Pharmaceuticals and Medical Devices Agency

1. Introduction

In order to promote safe use of pharmaceuticals and medical devices etc., a variety of safety information, including package inserts, are being provided on the pharmaceutical and medical devices information website ([<http://www.info.pmda.go.jp/>]). Notably, a wide range of information has been posted on the website since the establishment of the Pharmaceuticals and Medical Devices Agency in April 2004. This report introduces the background, and some of the main features.

2. Background, etc.

Since May 1999, the Organization for Pharmaceutical Safety and Research (at the time) had been providing information on the Pharmaceutical Information System, which existed prior to the Pharmaceutical and Medical Devices Information website, including the “Revision of PRECAUTIONS” issued by the Ministry of Health and Welfare (at the time), the “Pharmaceuticals and Medical Devices Safety Information”, “Dear Healthcare Professional Letters” issued by pharmaceutical companies, and other pharmaceutical safety information targeting physicians, dentists, and pharmacists.

The role of providing safety information of drugs was discussed in the “Council for the Pharmaceutical Information Service Scheme”, and a final report was issued in September 2001. It is recommended in this final report that “in order to ensure rapid provision of accurate and easy-to-understand information on drugs to healthcare providers, patients, and the general public, in a user-friendly form, it will be beneficial to expand/strengthen the current “Pharmaceutical Information System” and to establish a “Comprehensive Pharmaceutical Information Network”, based on 3 concepts utilizing IT, namely: ①the provision of comprehensive information, ②the provision of the latest information, and ③the provision of information to the general public.

Based on this final report, pharmaceutical and medical devices safety information such as the information on the approval of new drugs, recall information, and medical safety information have been added in the current Pharmaceutical and Medical Devices Information website, and the most up-to-date and comprehensive information are being provided. In particular, the provision of information to the general public is being strengthened in the recent years.

Moreover, the website has been renewed based on the opinions of the users obtained by the web questionnaire survey conducted in March 2006, etc. The display of information has been rearranged and some functions such as font enlargement have been strengthened, so that the users from the healthcare providers, general public and companies can use and search for the necessary information more easily.

In the future, it is planned to improve the quantity/quality of information by gradually expanding the range of information, such as the package inserts of IVD (in vitro diagnostics) etc.

3. Main contents that have been included since April 2004

(1) Line list of adverse reaction/adverse event reports

A line list of adverse reaction/adverse event reports is announced in order to inform the reports on

adverse reaction/adverse event to the public, including healthcare providers, and to inform the marketing authorisation holders of pharmaceuticals or medical devices so that they can review post-marketing safety measures by becoming aware of the line list of adverse reaction/adverse event reports not only of their own products but also of other company's products with the same active ingredients/nonproprietary name, as well as the line list of adverse reactions in which their own products are referred to as suspected concomitant medications.

All the adverse reaction/adverse event reported to PMDA by the marketing authorisation holders of pharmaceuticals and medical devices, since the establishment of PMDA in April 2004, are subject to announcement.

The announcement has started in January 2006 for the adverse drug reaction line list, and in March 2006 for the adverse event line list. By the end of March 2007, reports of up to March 2006 have been announced for both.

Moreover, the adverse reaction/adverse event reports include those where the causality between the pharmaceutical or medical devices and the adverse reactions or malfunctions is unclear. Therefore, for the cases which resulted in death, the announcement is also made on the result of evaluation for the causality between the death and the adverse reaction/adverse event.

(2) Information on package inserts of medical devices

Package inserts of the latest medical devices are provided, for appropriate and safe use of medical devices. It is possible to search by nonproprietary names/brand names, categories, approval number etc. and there is also a system to find the updated package inserts when revision of PRECAUTIONS is made. The operation has started in June 2005, and approximately 4000 package inserts have been posted as of the end of March 2007.

(3) Information on package inserts of over the counter drugs

Following the revision of the Pharmaceutical Affairs Law in June 2006, the package inserts of over the counter drugs are being provided on the website from March 2007, with the aim to provide information according to the level of risks, to develop counseling systems, to build the capacity of the marketing specialists of drugs, and to develop appropriate environment for the provision of information and counseling services. The system allows the search based on brand names, marketing authorization holders, dosage forms, active ingredients, and additives etc., making it possible for the patients etc. who are allergic to specific active ingredient to find certain products by searching/excluding particular ingredients or additives. For the moment, a package insert will be displayed in the form of an image in PDF files.

(4) Drug Guidance for Patients

Based on the recommendations of the "Council for the Pharmaceutical Information Service Scheme", assistance is given in the production of "Guidelines of Pharmaceuticals for Patients" which is provided for proper understanding of the ethical drugs in patients and early detection of clinically significant adverse reactions etc. The guidelines, approved by MHLW, are sequentially being posted since January 2006, and there are currently approximately 1100 types of "Drug Guidance for Patients" on the website, as of March 2007.

Furthermore, a "Drug Information Leaflet" provided by the Council for the Proper use of Ethical Drugs can also be searched from the retrieval screen of the Drug Guidance for Patients since March 2007.

Please refer to the Pharmaceuticals and Medical Devices Safety Information No. 222, for the details on the Drug Guidance for Patients.

(5) Manuals for Management of Individual Serious Adverse Drug Reactions

MHLW is preparing the manuals for serious drug-induced diseases targeted for adverse reactions

which may lead to serious conditions, focusing on the adverse reactions by the use of drugs over a 4-year period starting from 2006, with the cooperation of the relevant medical societies. From November 2006, 8 manuals have been provided on the website, namely: Stevens-Johnson syndrome, toxic epidermal necrosis, interstitial pneumonia, acute lung injury/acute respiratory distress syndrome, non-steroidal anti-inflammatory drug-induced asthmatic attack, drug-induced Parkinsonism, rhabdomyolysis, leukoencephalopathy, and pseudoaldosteronism.

The manuals include information which allow patients and family members to detect symptoms of clinically significant adverse reactions from the subjective symptoms at an early stage, as well as information for healthcare providers such as diagnostic methods and measures to be taken.

Please refer to the Pharmaceuticals and Medical Devices Safety Information No. 230, for the details on the Manuals for Management of Individual Serious Adverse Drug Reactions..

(6) Pharmaceutical and Medical Devices Information Distribution Service (Push type mailing service)

This is an information distribution service that sends out information to the registered e-mail addresses when relatively important safety information is issued, such as the Dear Healthcare Professional Letters, revision of PRECAUTIONS, Class 1 recall of pharmaceutical and medical devices etc. so that the physicians, pharmacists, and nurses etc. working on the medical sites need not actively search for the information. Registration to this service is expected to help in the prevention of hazards in public health and hygiene, by allowing the healthcare providers working on the site to rapidly obtain important safety information on pharmaceuticals and medical devices etc. The operation has started from August 2005, approximately 6500 registrations have been made as of the end of February 2007, and a total of 178 information have been distributed since inception.

(7) Information for the general public

As the information for the general public, the above-mentioned Drug Guide for Patients, Manuals for Management of Individual Serious Adverse Drug Reactions, and package inserts for over the counter drugs are provided, as well as the Q&A section which is the summary of questions that are frequently asked by the consumers through the counseling service for medicine and medical devices or the “medicine guidance” telephone service.

4. Closing comments

In order to improve the safety measures of pharmaceuticals and medical devices, it is necessary to provide information that is easy to understand and accessible to the users of the information i.e. the healthcare providers, general public and companies. It is hoped that many people will actively use the Pharmaceuticals and Medical Devices Agency website, and it would be grateful if suggestions for improvements etc., if any, can be sent to the Safety Information Division of the Office of Safety within PMDA (E-mail: info-master@pmda.go.jp).

4

List of products subject to Early Post-marketing Phase Vigilance

(As of April 1, 2007)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Olopatadine Hydrochloride ----- Patanol Ophthalmic Solution 0.1%	Alcon Japan Ltd.	October 5, 2006
Busulfan ----- Busulfex Injection 60 mg	Kirin Brewery Company, Limited	October 10, 2006 ^{*1} October 20, 2006 ^{*2}
Fexofenadine Hydrochloride ----- Allegra Tablets 60 mg ^{*3}	Sanofi-Aventis K.K.	October 20, 2006
Landirolol Hydrochloride ----- Onoact 50 for Injection ^{*4}	Ono Pharmaceutical Co., Ltd.	October 20, 2006
Mozavaptan Hydrochloride ----- Physuline Tablets 30 mg	Otsuka Pharmaceutical Co., Ltd.	October 24, 2006
Interferon Beta-1a (Genetical recombination) ----- Avonex IM Injection Syringe 30 µg	Biogen Idec Japan Ltd.	November 6, 2006
Moxifloxacin Hydrochloride ----- Vegamox Ophthalmic Solution 0.5%	Alcon Japan Ltd.	November 6, 2006
Pneumococcal Vaccine ----- Pneumovax NP	Banyu Pharmaceutical Co., Ltd.	November 29, 2006
Bortezomib ----- Velcade Injection 3 mg	Janssen Pharmaceutical K.K.	December 1, 2006
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%, 1%, 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 Pharmaceutical 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* ⁵	Tanabe Seiyaku Co., Ltd.	January 26, 2007
Zanamivir Hydrate Relenza* ⁶	GlaxoSmithKline K.K.	January 26, 2007
Tacrolimus Hydrate Prograf Capsules 0.5 mg and 1 mg* ⁷	Astellas Pharma Inc.	January 26, 2007
Baclofen Intrathecal Gabalon 0.005%, 0.05%, and 0.2%* ⁸	Daiichi Pharmaceutical Co., Ltd.	January 26, 2007
Micafungin Sodium Funguard 25 mg, 50 mg, and 75 mg for Infusion* ⁹	Astellas Pharma Inc.	January 26, 2007
Ruriocog 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* ¹⁰	Nippon Organon K.K.	March 16, 2007
Peginterferon Alpha-2a (Genetical recombination) Pegasys s.c. 90 µg and 180 µg* ¹¹	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Ribavirin Copegus Tablet 200 mg	Chugai Pharmaceutical Co., Ltd.	March 16, 2007
Modafinil Modiodal Tablets 100 mg	Alfresa Parma Corporation	March 28, 2007

- *1: For the adult dose initially approved
- *2: An additional administration for “pediatrics”
- *3: An additional administration for “pediatrics” (aged 7 and older)
- *4: An additional indication for “emergency measures against following tachycardiac arrhythmia occurring under post-operative monitoring of circulatory dynamics: atrial fibrillation, atrial flutter, sinus tachycardia”
- *5: 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)”
- *6: An additional indication for “the prophylaxis of influenza A or B virus infection”
- *7: An additional indication for “Lupus nephritis (in case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions)”
- *8: An additional administration for “pediatrics”
- *9: An additional indications for “Prophylaxis of Aspergillus and Candida infections in patients undergoing hematopoietic stem cell transplantation”
- *10: An additional indication for “the ovulation induction in patients with anovulation or infrequent ovulation associated with hypothalamic-pituitary dysfunction”
- *11: An additional indication for “the use in combination with ribavirin, for the improvement of viraemia in one of the following chronic hepatitis C: (1) serogroup 1 (genotype I (1a) or II (1b)) with high serum HCV-RNA loads, or (2) patients who failed interferon monotherapy or who developed reactivation (of chronic hepatitis C) following interferon monotherapy”

Reference Material 1

Oseltamivir Phosphate

Regarding Oseltamivir phosphate, the following reference materials introduce the instruction to issue the Dear Healthcare Professional Letters dated March 20, 2007, in relation to “Abnormal behaviour after the administration of Tamiflu” and the report of Pharmaceutical Affairs and Food Sanitation Council, Committee on Drug Safety, Subcommittee on Drug Safety Committee, dated April 4, 2007, entitled “the opinions on the current responses to the issue of Oseltamivir phosphate (Tamiflu) based on the reports of adverse reactions etc.”.

Abnormal behaviour after the administration of Tamiflu (instruction to issue the Dear Healthcare Professional Letters)

1. Product description

Nonproprietary Name:	Oseltamivir phosphate
Brand Name: (indications)	① Tamiflu Capsule 75 (Treatment or prophylaxis of viral infection of influenza A and B) ② Tamiflu dry syrup 3% (Viral infection of influenza A and B)
Therapeutic Category:	Antivirals
Marketing Authorisation Holder:	Chugai Pharmaceutical Co., Ltd.
Domestic Supply:	For approximately 8.6 million people (winter season of 2005)

2. Background

- (1) Oseltamivir phosphate (Tamiflu) is an oral formulation indicated for viral infection of influenza A or B (capsules include the indication for the prevention). In Japan, its marketing started in February 2001.
- (2) Although the causality between Tamiflu and “psychological/neurological symptoms” is unclear, on May 2004, the following statement was added under the section “Clinically significant adverse reactions” in the package insert, in order to alert the healthcare providers: “Psychoneurological symptoms (e.g. disturbances in consciousness, abnormal behaviour, delirium, hallucination, delusion, convulsions) may occur. If any abnormality is observed, the administration should be discontinued. Patients should be carefully monitored and appropriate therapeutic measures should be taken according to individual symptoms”.
- (3) In February this year, 2 tragic cases have been reported in the media where 2 junior high school students, who were thought to have taken Tamiflu, fell from their apartment and died. As preventive measures to avoid any possible accidents during recuperation at home, especially for children/minors, once the patient is diagnosed with influenza and the treatment is initiated with or without the prescription of Tamiflu, it will be appropriate ① to explain about the possible occurrence of abnormal behavior, ② for guardians to be mindful not to leave the children/minors by themselves for at least 2 days. Healthcare providers involved in the treatment of influenza have been reminded on February 28, to provide appropriate explanation to the patient and family members.
- (4) Although preventive measures such as those mentioned above in (3) had been taken, 1 case of fracture of a patient aged 12 falling from the second floor after the administration of Tamiflu, was reported today (March 20). Furthermore, a case of fracture that had occurred in early February concerning a patient aged 12 falling from the second floor after the administration of Tamiflu, was also reported today (March 20).

The evaluation of these individual cases will be made based on detailed information to be collected from now on; however, as it has been confirmed that these events occurred after the administration of Tamiflu, revisions of the package inserts have been made, Dear Health Professional Letters have been distributed to medical institutions, etc., and instructions have been given to Chugai Pharmaceutical Co., Ltd. to call for the further attention of healthcare providers regarding the occurrence of abnormal behaviours after the administration of Tamiflu.

3. Responses

(1) MHLW

MHLW has instructed Chugai Pharmaceutical Co., Ltd. to revise the package inserts, prepare and distribute Dear Healthcare Professional Letters to medical institutions, etc.

(2) Chugai Pharmaceutical Co., Ltd.

a. Distribute Dear Healthcare Professional Letters and ensure that the revisions made on the package inserts, as described in b. below, are promptly communicated to the medical institutions etc.

b. Revisions of the package insert

Modify the current "Warning" section as follows, with the addition of appropriate PRECAUTIONS.

[Tamiflu Capsules 75]

1. The necessity of TAMIFLU for treatment should be carefully examined before use.

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

Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

3. Prophylaxis of influenza viral infections is based on vaccine therapy. Note that the prophylactic use of TAMIFLU is not an alternative to vaccine therapy.

[Tamiflu Dry Syrup 3%]

1. The necessity of TAMIFLU for treatment should be carefully examined before use.

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

Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

3. TAMIFLU Dry Syrup is not recommended for prophylactic use.

[References: contact of marketing authorisation holder]

Chugai Pharmaceutical Co., Ltd.
Pharmaceutical Information Center
TEL: 0120-189-706

(Reference)

Safety Division of the Pharmaceutical and Food Safety Bureau
TEL: 03-5253-1111
Extension 2749

The opinions on the current response to Oseltamivir Phosphate (Tamiflu), based on the reports of adverse reactions

The opinions on the current response to the issue of Tamiflu, are as follows.

1. Today's discussions

This subcommittee reviewed today, the reports from companies on 1079 people, 1465 cases of adverse reactions, collected by March 20, 2007, and the adverse reactions of 185 people (unprocessed) reported from companies between March 21 to April 3, 2007.

From today's review, conclusion was not reached regarding the relation between the administration of Tamiflu and falls/jumping off, or adverse reactions such as abnormal behaviour leading to these events, or sudden deaths.

A more detailed review and efforts such as those described in 3, are required.

2. Measures that are being taken at present

1 Dear Healthcare Professional letter was issued on March 20 and the following measures are currently being taken. It will be appropriate to continue these measures for now, but further efforts should be made to call for the attention to healthcare professionals etc. and to disseminate the basic information on influenza etc. to patient/family members.

Current measures will be reviewed further by a working group which will be newly established.

- The administration of this drug should be avoided in patients aged between 10 and 19, unless he/she is considered as a high-risk patient based on complications and medical history.
- When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, abnormal behaviour may occur and caregivers should be careful not to let patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents including falls due to abnormal behaviour.
- Also, since it has been reported that similar symptoms occur due to influenza encephalopathy, it is required to explain the same as above.

2 Falls/jumping off or manifestation of abnormal behaviour leading to such events have been observed during the clinical course of influenza, even without the administration of Tamiflu.

Healthcare providers should be aware of this, and relevant organization should call for attention to healthcare providers.

3. Measures which need to be taken in the future

1 It is appropriate to conduct the following basic research and report the result to this subcommittee, in order to contribute to the clarification of the issue.

- About the transfer of Tamiflu into the brain (central nervous system) etc. in order to further clarify the neurophysiological effect of Tamiflu

2 It is appropriate to establish ①a working group for the clinical investigation of Tamiflu (tentative name) (hereafter referred to as the “clinical WG”), and ②a working group for the basic investigation of Tamiflu (tentative name) (hereafter referred to as the “non-clinical WG”) as subsidiary organization of this subcommittee, in order to undertake detailed investigative review in the following clinical and basic aspects of the safety of Tamiflu, and to report the results to the investigative committee.

① Clinical WG

- A detailed investigative review of the adverse reactions including falls/jumping off, abnormal behaviours leading to such events, or sudden deaths, as well as a review of presence or absence of problems specific to the high risk patients of influenza infection.
- The review of clinical research plans, results etc.
- The review of the result of “The research on the manifestation of influenza-associated symptoms” funded by Ministry of Health, Labour and Welfare Grants for FY2006.

② non-clinical WG

- The review of basic research plans, results etc.

3 The result of “The research on the manifestation of influenza-associated symptoms” funded by Ministry of Health, Labour and Welfare Grants for FY2006, will be reported to the clinical WG and this subcommittee.

4 The companies and MHLW should continue to collect domestic and international safety information on Tamiflu, and take prompt and appropriate measures as necessary.

Overview of Pharmacogenomics (Genetic polymorphism related to warfarin therapy)

1. Introduction

Pharmacogenomics plays an important role in understanding genetic factors in each patient regarding potential difference in drug efficacy and risks for adverse reactions, and the current situation in this field has been described in the reference material of the Pharmaceuticals and Medical Devices Safety Information No. 219.

At ICH (the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), progress is being made on the development of the basis of pharmacogenomics, such as the development of guidelines clarifying the definitions of the relevant technical terms¹⁾. As a topic on pharmacogenomics, this report will introduce the issue on genetic polymorphism related to warfarin therapy.

2. Genetic polymorphism related to warfarin therapy

Warfarin is an oral anticoagulant, which has been widely used for the treatment and prevention of thromboembolism, not only in Japan but also internationally. There is a large difference in dosage among individuals, and it has been considered as one of the drugs for which the estimation of the dose for initial administration is difficult. The target molecule of warfarin is vitamin K epoxide reductase complex subunit 1 (VKORC1), which is involved in the production of vitamin K-dependent coagulation factor, and cytochrome P450 2C9 (CYP2C9) is the main metabolic enzyme of S-warfarin that shows pharmacological effects.

Recent studies reported genetic polymorphisms of VKORC1 and CYP2C9, and were finding evidence supporting that these genetic polymorphisms are associated with therapeutic effect of warfarin.

It is said that the dosage of warfarin is low for the patients with type H1 and H2 of VKORC1, and that there is a tendency of patients with type H7, H8 and H9 to require higher dosage²⁾.

While the patients with CYP2C9 variant require low dosage but has a higher risk of haemorrhage occurring as adverse reaction due to their low warfarin metabolism, the patients with wild type are said to require higher dose of warfarin³⁾.

Ethnic difference has been reported regarding the incidence of genetic polymorphism related to warfarin therapy. It has been reported that the incidence of H1 and H2 types of VKORC1 that are thought to be warfarin-sensitive, is high in Asians with approximately 90%, compared to approximately 40% in Europeans and approximately 10% in Africans. Meanwhile CYP2C9 genetic polymorphism that inhibits warfarin metabolism is said to occur in less than 5% of Japanese, which is not high compared to 1% to 20% occurrence in other races⁴⁾. It can be predicted that Japanese people are relatively sensitive to warfarin and many require low dosage.

CYP2C9 is related to the metabolism of many drugs. Concomitant treatment with phenytoin delays warfarin metabolism and increase its blood concentration, therefore, attention should be paid to concomitant medications when undertaking warfarin therapy.

From the above reasons, it can be said that VKORC1 and CYP2C9 genetic polymorphism may provide important information in deciding the optimum dosage of warfarin. It is hoped that further researches on the relationship between genetic polymorphism and warfarin-sensitivity will be

conducted in Japan.

Table. Warfarin related genetic polymorphism

Genetic polymorphism	Haplotype etc.	Warfarin-sensitivity
VKORC1	H1, H2	High
	H7, H8, H9	Low
CYP2C9	Variant	High
	Wild type	Low

3. Future perspectives

The test agent for UGT1A1 genotype polymorphism, related to the manifestation of serious adverse reaction of irinotecan hydrochloride, has been approved as IVD drug in the US and references for the adjustment of dosage is indicated on the package inserts. In Japan, MHLW has requested the related companies to implement its development and practical application, and the marketing authorisation holder is currently applying for the approval of the test agent for UGT1A1 genetic polymorphism, which is related to the adverse reaction of irinotecan hydrochloride. Even if gene analysis was established at research level, there are many problems to be solved in order to practice personalized medical care utilizing pharmacogenomics⁵. While international efforts are being made in the field of pharmacogenomics, further development in the realization of a more effective/safer pharmacotherapy will be expected in the future.

<References>

- 1) Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories (draft) ICH E15 Guideline (2006)
- 2) Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med*, 352 (22):2285-93 (2005)
- 3) Aithal GP, Day CP, Kesteven PJ, Daly AK : Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet*, 353: 717-9 (1999)
- 4) Hirotochi Echizen: Genetic polymorphism related to interindividual variation of the anticoagulation effect of warfarin. *J Thromb Haemost* 12 (2):111-8 (2001) (In Japanese)
- 5) Natatani: Personalized medicine in antithrombotic regimen *Journal of Japanese Society on Thrombosis and Hemostasis* 17 (6): 706-10 (2006) (In Japanese)