Pharmaceuticals and Medical Devices Safety Information

No. 309 January 2014

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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 (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers.
The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page] (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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

Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

Pharmaceuticals and Medical Devices Safety Information
No. 309 January 2014

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Precautions for Use of Puncture Site Closure Devices**		Cases of serious malfunctions have been reported regarding puncture site closure devices that are used for hemostasis at the site of catheterization (site of femoral artery puncture) for percutaneous transluminal angioplasty or other procedures. This section provides information on the malfunctions reported in Japan, as well as precautions for patient care and other procedures during and after using closure devices.	5
2	**List of Products Subject to Early Post-marketing Phase Vigilance**		Lists products subject to Early Post-marketing Phase Vigilance as of January 1, 2014.	9
Reference	**Drugs and Medical Devices Safety Information Reporting System**		Healthcare professionals are encouraged to report to the MHLW about adverse reactions or device malfunctions of not only drugs and medical devices but also quasi-drugs and cosmetics.	12

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

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADRs	Adverse drug reactions
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing authorization holder
FY	Fiscal year
VCDs	Vascular closure devices
MHLW	Minister of Health, Labour and Welfare
PFSB	Pharmaceutical and Food Safety Bureau

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Precautions for Use of Puncture Site Closure Devices

1. Introduction

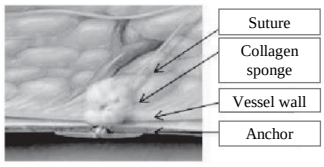
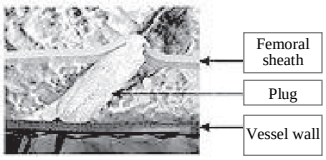
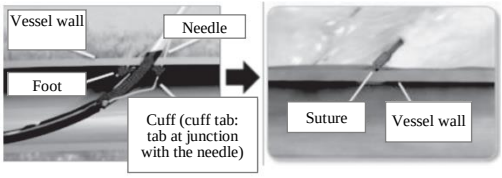
Manual or other types of pressure hemostasis are performed conventionally at the site of femoral artery puncture (site of catheterization) after treatment using percutaneous transluminal angioplasty or other procedures. Since pressure hemostasis takes several hours, however, medical devices to achieve hemostasis of the puncture site ("puncture site closure devices" or "vascular closure devices," hereinafter referred to as "VCDs") have been also widely used in order to reduce bed rest time for hemostasis and to avoid peripheral circulatory failure caused by pressure.

Precautions for patient care and other procedures during and after using a VCD are included in the package insert, user's manual, etc. for the device, but cases of serious malfunctions due to the VCD have been reported. Information on these cases reported to PMDA and the relevant precautions are described below.

2. Types of VCDs

6 VCD products have been marketed from 4 marketing authorization holders (MAHs). According to the mechanism of hemostatic method, these devices are divided into two types: (1) Products to stop bleeding by blocking off the outside of the vascular wall at the puncture site with a bioabsorbable material (collagen or polyglycolic acid) (hereinafter referred to as "absorbable topical hemostatic material") and (2) products to directly suture the vascular wall at the puncture site with a non-absorbable suture (hereinafter referred to as "non-absorbable suture set") (See **Table 1**).

Table 1. Types of VCDs

<table>
<tr><td colspan="2">(1) Absorbable topical hemostatic material</td><td>(2) Non-absorbable suture set</td></tr>
<tr><td>Angio-Seal STS PLUS
(St. Jude Medical Japan Co., Ltd.)</td><td>EXOSEAL
(Johnson & Johnson K.K.)</td><td>Perclose ProGlide
(Abbott Vascular Japan Co., Ltd.)</td></tr>
<tr><td> 
</td><td> 
</td><td> 
</td></tr>
<tr><td>Source) Product package insert</td><td>Source) Product package insert</td><td>Source) Explanatory material on summaries of product characteristics by the manufacturer</td></tr>
</table>

3. Occurrence status of malfunctions

A total of 305 cases of malfunctions for VCDs have been reported to PMDA from April 2004 to the end of September 2013 in Japan. A list of them is shown in Table 2.

(1) Malfunctions of absorbable topical hemostatic materials

Major malfunctions of absorbable topical hemostatic materials are "false aneurysm," "retroperitoneal hematoma," "hemostatic failure (bleeding)," and "vascular stenosis (occlusion)" after the use of the device. Among them, "false aneurysm," "retroperitoneal hematoma," and "hemostatic failure (bleeding)" have been reported to occur for reasons such as that the absorbable hemostatic material does not appropriately adhere to the vessel wall due to calcification, flexure, etc. of the blood vessels at the insertion site of the femoral artery. In addition, "vascular stenosis (occlusion)" is considered to occur because a part of the absorbable hemostatic material is deposited into the blood vessel and becomes swollen inside the blood vessel.

These malfunctions characteristically occur in a delayed manner after hemostatic treatment. There are occasionally cases where a change in the patient's condition leads to the detection of malfunctions and there is difficulty in subsequent treatment, resulting in serious outcomes including death for which a causal relationship with the devices cannot be ruled out.

(2) Malfunctions, etc. of non-absorbable suture sets

Major malfunctions of non-absorbable suture sets are cases where a component (foot, cuff tab, etc.) of the device is damaged during manipulation. Breakage of components has been reported to occur for reasons such as that calcification, flexure, etc. of the blood vessels at the insertion site of the femoral artery interfere with the proper operation of components, thereby producing an overload.

Meanwhile, for non-absorbable suture sets, there are occasionally cases where the procedure time is prolonged due to breakage during manipulation, so measures such as switching to manual pressure on the spot are taken but it cannot be ruled out that the fragment may remain in the body.

Table 2. List of malfunctions of VCDs reported in Japan

(1) Absorbable topical hemostatic materials

Product name (company name)	Malfunction/adverse event	Number of reported events[*1]	Total[*1]	Sales figure[*2] Sales period
Angio-Seal Millennium Platform (MP) (St. Jude Medical Japan Co., Ltd.)	Hemostatic failure (bleeding) Puncture site hematoma Vascular stenosis (occlusion) False aneurysm Postoperative infection Retroperitoneal hematoma Deployment failure Vascular injury (perforation, dissociation) Puncture site swelling Allergic reaction	38 21 19 12 (1) 10 (1) 9 (5) 9 3 3 2	126 (7)	Approximately 120,000 units September 2003 - April 2008
Angio-Seal STS PLUS (St. Jude Medical Japan Co., Ltd.)	Vascular stenosis (occlusion) Puncture site hematoma Hemostatic failure (bleeding) False aneurysm Retroperitoneal hematoma Postoperative infection Deployment failure Puncture site swelling	35 (1) 16 (1) 15 (1) 13 (1) 8 (1) 6 4 2	99 (5)	Approximately 310,000 units June 2007 -
Angio-Seal Evolution (St. Jude Medical Japan Co., Ltd.)	False aneurysm Puncture site hematoma Hemostatic failure (bleeding) Vascular stenosis (occlusion) Retroperitoneal hematoma Puncture site swelling	3 2 1 1 1 1	9 (0)	Approximately 20,000 units September 2009 -
EXOSEAL (Johnson & Johnson K.K.)	Deployment failure Puncture site hematoma Hemostatic failure (bleeding) Vascular injury (perforation, dissociation) False aneurysm	8 2 (1) 2 2 2	16 (1)	Approximately 16,000 units September 2012 -

(2) Non-absorbable suture sets

Product name (company name)	Malfunction/adverse event	Number of reported events[*1]	Total[*1]	Sales figure[*2] Sales period
Perclose A-T (Terumo Corporation)	Breakage of component (including remnants in the body) Puncture site swelling Vascular stenosis (occlusion) False aneurysm Vascular injury (perforation, dissociation) Retroperitoneal hematoma	23 3 3 2 1 1	33 (0)	Approximately 41,000 units November 2004 - November, 2011
Perclose ProGlide (Abbott Vascular Japan Co., Ltd.)	Breakage of component (including remnants in the body) Vascular stenosis (occlusion) Closure failure Puncture site pain False aneurysm Postoperative infection	12 4 3 1 1 1	22 (0)	Approximately 28,000 units December 2009 -

*1 Number of events in parentheses indicates the number of cases of death in the reported events, including cases where a causal relationship between an observed malfunction/adverse event and death cannot be denied.

*2 The sales figure at the MAHs is different from the actual number of units used.

4. Safe use of VCDs

Diagnosis or treatment with catheters may become increasingly common, and along with such increases, opportunities for the use of VCDs may be increased.

Results of meta-analysis to compare VCDs and manual and other types of pressure hemostasis overseas show that there was no significant difference in incidence of malfunctions, etc., but false aneurysm, hematoma, bleeding, etc. occurred at a rate of 4.7% to 5.7% in VCDs [1), 2)]. The number of malfunction reports in Japan was as shown in **Table 2**, but the occurrence frequency of similar events in Japan is unknown because it has not been sufficiently investigated, and therefore it is necessary to pay sufficient attention to the occurrence of these events.

In order to avoid serious malfunctions including death in association with treatment of the puncture site after catheterization, etc., as much as possible, healthcare professionals are encouraged to sufficiently evaluate the status of the blood vessel at the catheter insertion site (puncture site) (atherosclerosis lesion, calcification lesion, etc.) or anatomical characteristics (bifurcation region, flexural region, etc.), and renal impairment, which is a risk factor for complications such as bleeding and infection (including cases during dialysis) [3)], and then select a method of hemostasis. In addition, in preparation for delayed malfunctions, etc., healthcare professionals should instruct the patient to take a bed rest for a certain time or avoid movements which cause pressure at the hemostasis site and sufficiently monitor the patient's vital signs (blood pressure, pulse rate, etc.) and symptoms in the lower extremities (numbness, feeling cold, pain, swelling, etc.).

The MAHs who handle VCDs provide information through package inserts and other materials and also conduct hands-on seminars, etc. Please utilize them for the proper use and improvement of manipulation/procedures for the relevant device(s).

<References>

1) Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. *JAMA* 2004; 291(3): 350-357
2) Arterial closure devices versus manual compression for femoral haemostasis in interventional radiological procedures: a systematic review and meta-analysis. *Cardiovasc Intervent Radiol* 2011; 34(4): 723-738
3) Arteriotomy closure devices for cardiovascular procedures: a scientific statement from the American Heart Association. *Circulation* 2010; 122(18): 1882-1893

2

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of new drugs. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of January 1, 2014)

◎: Newly-posted products, or products changed from the last Bulletin

	Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
◎	Meropenem Hydrate (1) Meropen Vial for Intravenous Drip Infusion 0.25 g, 0.5 g (2) Meropen Kit for Intravenous Drip Infusion 0.5 g*1	Dainippon Sumitomo Pharma Co., Ltd.	December 20, 2013
◎	Methylphenidate Hydrochloride Concerta Tablets 18 mg, 27 mg*2	Janssen Pharmaceutical K.K.	December 20, 2013
◎	Laninamivir Octanoate Hydrate INAVIR DRY POWDER INHALER 20 mg*3	Daiichi Sankyo Company, Limited	December 20, 2013
◎	Fentanyl OneDuro Patch 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, 6.7 mg*4	Janssen Pharmaceutical K.K.	December 20, 2013
◎	Vilanterol Trifenatate/Fluticasone Furoate Relvar 100 Ellipta 14 doses, Relvar 200 Ellipta 14 doses	GlaxoSmithKline K.K.	December 9, 2013
◎	Talc Unitalc Intrapleural 4 g	Nobelpharma Co., Ltd.	December 9, 2013
◎	Simeprevir Sodium SOVRIAD capsules 100 mg	Janssen Pharmaceutical K.K.	December 6, 2013
	Epinastine Hydrochloride ALESION Ophthalmic Solution 0.05%	Santen Pharmaceutical Co., Ltd.	November 25, 2013
	Acetaminophen acelio Intravenous Injection 1000 mg	Terumo Corporation	November 25, 2013
	Landiolol Hydrochloride ONOACT 50 for Injection*5	Ono Pharmaceutical Co., Ltd.	November 22, 2013
	Aflibercept (Genetical Recombination) EYLEA solution for IVT inj. 40 mg/mL*6, EYLEA solution for IVT inj. Kit 40 mg/mL*6	Bayer Yakuhin, Ltd.	November 22, 2013
	Topiramate TOPINA Tablets 25 mg, 50 mg, 100 mg*7	Kyowa Hakko Kirin Co., Ltd.	November 22, 2013
	Indacaterol Maleate/Glycopyrronium Bromide ultibro inhalation capsules	Novartis Pharma K.K.	November 20, 2013

	Tafamidis Meglumine Vyndaqel capsules 20 mg	Pfizer Japan Inc.	November 20, 2013
	Fluticasone Propionate/Formoterol Fumarate Hydrate Flutiform 50 Aerosol 56 puffs, 125 Aerosol 56 puffs	Kyorin Pharmaceutical Co., Ltd.	November 19, 2013
	Brinzolamide/Timolol Maleate AZORGA Combination Ophthalmic Suspension	Alcon Japan Ltd.	November 19, 2013
	Paliperidone Palmitate XEPLION Aqueous Suspension for IM Injection Syringe 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Janssen Pharmaceutical K.K.	November 19, 2013
	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) Prevenar13 Suspension Liquid for Injection	Pfizer Japan Inc.	October 28, 2013
	Hydroxyethylated Starch 130000 VOLUVEN 6% solution for infusion	Fresenius Kabi Japan K.K.	October 25, 2013
	Fentanyl Citrate E-fen buccal tablet 50 μg, 100 μg, 200 μg, 400 μg, 600 μg, 800 μg	Teikoku Seiyaku Co., Ltd.	September 26, 2013
	Norethisterone/Ethinylestradiol LUNABELL tablets ULD	Nobelpharma Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride ALAGLIO Oral 1.5 g	SBI Pharmaceuticals Co., Ltd.	September 26, 2013
	Aminolevulinic Acid Hydrochloride Alabel Oral 1.5 g	Nobelpharma Co., Ltd.	September 18, 2013
	Lixisenatide Lyxumia Subcutaneous Injection 300 μg	Sanofi K.K.	September 17, 2013
	Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 μg PLASTIC SYRING, 15 μg PLASTIC SYRINGE, 20 μg PLASTIC SYRINGE, 30 μg PLASTIC SYRINGE, 40 μg PLASTIC SYRINGE, 60 μg PLASTIC SYRINGE, 120 μg PLASTIC SYRINGE, 180 μg PLASTIC SYRINGE*[8]	Kyowa Hakko Kirin Co., Ltd.	September 13, 2013
	Tolvaptan Samsca tablets 7.5 mg*[9]	Otsuka Pharmaceutical Co., Ltd.	September 13, 2013
	Eculizumab (Genetical Recombination) Soliris Drip Infusion 300 mg*[10]	Alexion Pharma G.K.	September 13, 2013
	Pertuzumab (Genetical Recombination) PERJETA Intravenous Infusion 420 mg/14 mL	Chugai Pharmaceutical Co., Ltd.	September 12, 2013
	Bisoprolol Bisono tape 4 mg, 8 mg	Toa Eiyo Ltd.	September 10, 2013
	Irbesartan/Trichlormethiazide Irtra Combination Tablets LD, HD	Shionogi & Co., Ltd.	September 4, 2013
	Topiroxostat (1) TOPILORIC Tablets 20 mg, 40 mg, 60 mg (2) URIADEC Tab. 20 mg, 40 mg, 60 mg	(1) Fujiyakuhin Co., Ltd. (2) Sanwa Kagaku Kenkyusho CO., LTD.	September 4, 2013
	Ibandronate Sodium Hydrate Bonviva IV Injection 1 mg Syringe	Chugai Pharmaceutical Co., Ltd.	August 29, 2013
	Abatacept (Genetical Recombination) ORENCIA SYRINGE FOR S.C. INJECTION 125 mg/1 mL	Bristol-Myers K.K.	August 27, 2013

	Hemin Normosang Infusion 250 mg	Orphan Pacific, Inc.	August 23, 2013
	Palivizumab (Genetical Recombination) Synagis for Intramuscular Injection 50 mg, 100 mg*[11] Synagis Intramuscular Solution 50 mg, 100 mg*[11]	AbbVie G.K.	August 20, 2013
	Ranibizumab (Genetical Recombination) LUCENTIS solution for intravitreal injection 2.3 mg/0.23 mL*[12]	Novartis Pharma K.K.	August 20, 2013
	Omalizumab (Genetical Recombination) Xolair for s.c. injection 150 mg, 75 mg*[13]	Novartis Pharma K.K.	August 20, 2013
	Tofacitinib Citrate XELJANZ Tablets 5 mg	Pfizer Japan Inc.	July 30, 2013
	Metreleptin (Genetical Recombination) Metreleptin for Subcutaneous Injection 11.25 mg "SHIONOGI"	Shionogi & Co., Ltd.	July 25, 2013
	Saxagliptin Hydrate ONGLYZA Tablets 2.5 mg, 5 mg	Kyowa Hakko Kirin Co., Ltd.	July 9, 2013

*1 An additional administration for "pyogenic meningitis"

*2 An additional administration for "patients aged 18 years or older"

*3 An additional indication for "the prevention of influenza A or B virus infection"

*4 An additional indication for "the treatment of patients with the following analgesia cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (only in patients who switch from an opioid analgesic): moderate to severe chronic pain"

*5 An additional indication for "the treatment of tachyarrhythmia including atrial fibrillation and atrial flutter in patients with failed cardiac function"

*6 An additional indication for "the treatment of patients with macular oedema following central retinal vein occlusion"

*7 An additional administration for "pediatrics"

*8 An additional administration for "pediatrics"

*9 An additional indication for "the treatment of fluid retention in patients with hepatic cirrhosis which is not adequately responded to other diuretics such as loop diuretics"

*10 An additional indication for "the treatment of patients with atypical hemolytic uremic syndrome to inhibit thrombotic microangiopathy"

*11 An additional indication for "the prevention of serious lower respiratory tract disease caused by respiratory syncytial (RS) virus infection in neonates and infants aged ≤24 months with immunodeficiency or Down syndrome (early stage of an epidemic of RS viral infection)"

*12 An additional indication for "the treatment of patients with macular oedema following retinal vein occlusion or choroidal neovascularization following pathologic myopia"

*13 An additional administration for "pediatrics"

Drugs and Medical Devices Safety Information Reporting System

Reports of adverse health effects, etc. (adverse reactions, infections, and malfunctions) due to drugs, medical devices, quasi-drugs, and cosmetics from medical institutions, etc. are important because healthcare professionals directly report adverse reactions, etc., to the MHLW so that data on the occurrence of adverse reactions, etc. will be promptly collected and adverse reactions, etc. that have not yet been grasped by MAHs will be detected.

Regarding reports of adverse health effects, etc., related to drugs or medical devices from healthcare professionals, understanding and cooperation have been gained as the Drugs and Medical Devices Safety Information Reporting System in accordance with the Pharmaceutical Affairs Law Article 77-4-2, Paragraph 2. The reported information has been provided to MAHs, etc. and analyzed, evaluated, and investigated to take necessary safety measures from specialist's point of view, and has been widely provided to healthcare professionals to secure post-marketing safety measures for drugs and medical devices.

The Drugs and Medical Devices Safety Information Reporting System is intended for drugs and medical devices. However, if any information on adverse health effects, etc. is obtained for quasi-drugs and cosmetics, healthcare professionals are encouraged to report the information using a drug safety information report form, in addition, to cooperate for information collection activities conducted by MAHs.

[References]

1. To Healthcare Professionals (A request for reports of adverse reaction/infection/malfunctions)
   http://www.info.pmda.go.jp/info/houkoku.html (only available in Japanese language)
   (The designated report form is available here)
2. Pharmaceutical Affairs Law Article 77-4-2, Paragraph 2
   When proprietors of pharmacies, hospitals, clinics or veterinary clinics, or physicians, dentists, pharmacists, registered salespersons, veterinarians or other healthcare professionals become aware of cases of diseases, disabilities or deaths possibly caused by adverse drug reactions or other reasons related to drugs or medical devices, or cases of infection possibly caused by the use of drugs or medical devices, and they consider that reporting of those cases is necessary to prevent the onset or spread of hazards to public health, they must report these cases to the MHLW.
3. The Pharmaceutical and Food Safety Bureau Notification No. 0824-4, by the Director of the PFSB, MHLW, dated August 24 2011 "Reporting of adverse health effects associated with the use of quasi-drugs or cosmetics" (only available in Japanese language. The title is provisionally translated.)

Reports of adverse reactions, etc. have been received via e-mail from March 2013 in addition to reports via fax, postal mail and "e-Gov" electronic application system.

Number of drugs and medical devices safety information reports received

	Drugs		Medical Devices	
	Fax/Postal mail	e-Gov/e-mail	Fax/Postal mail	e-Gov/e-mail
FY 2010	3655	0	368	0
FY 2011	3382	0	384	0
FY 2012	3276	28	515	2
FY 2013	2538	481	264	125

*Those received by the end of December 2013