Ministry of Health, Labour and Welfare

Safety Division, Pharmaceutical and Food Safety Bureau

Translated by **Pharmaceuticals and Medical Devices Agency**

Office of Safety I

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Notification

PFSB/ELD/OMDE Notification No. 0728-1
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To: Commissioner of Prefectural Health Department (Bureau)

Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW)
(Evaluation and Licensing of Medical Device/Cellular and Tissue-based Products)

Director of Safety Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Revision of the "PRECAUTIONS" in the package insert of Drug-eluting coronary stent or Drug-coated balloon dilatation catheter for coronary angioplasty

Upon the use of a drug-eluting coronary stent or a drug-coated balloon dilatation catheter for coronary angioplasty, ticlopidine hydrochloride, concomitantly used as an antiplatelet therapy, may cause thrombotic thrombocytopenic purpura (TTP), agranulocytosis, serious liver damage, etc. To prevent occurrence of such serious adverse reactions, advisory information has been included in the package insert of these products for ensuring the careful use of them.

Because prasugrel hydrochloride, another thienopyridine antiplatelet, was recently approved to have the same indication as ticlopidine hydrochloride and clopidogrel sulfate, the "PRECAUTIONS" in the package insert of drug-eluting coronary stent or drug-coated balloon dilatation catheter for coronary angioplasty are to be revised (e.g., the conventional detailed descriptions on antiplatelet drugs are summarized in a sentence: "Be sure to read the package insert of the antiplatelet drug to be concomitantly used."), in consideration of the use status and the occurrence of adverse reactions of ticlopidine hydrochloride.

Meanwhile, there have been reports on the occurrence of interstitial pneumonia in patients in whom drug-eluting coronary stents were placed. The association of the occurrences with stent placement cannot be ruled out, and the occurrences were reported on every drug that is used for a drug-eluting coronary stent or a drug-coated balloon dilatation catheter for coronary angioplasty currently approved. Therefore, the "PRECAUTIONS" are to be revised.

This notification is issued to advise the Marketing Authorization Holders dealing with these products to revise the "PRECAUTIONS" in the respective package insert as explained in Supplement.

With enforcement of this notification, the following notifications shall be abolished: “Proper use of Cypher stents” dated July 30, 2004 (PFSB/ELD Notification No. 0730001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and PFSB/SD Notification No. 0730001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW); “Proper use of Cypher stents” dated January 14, 2005 (PFSB/SD Notification No. 0114005 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW); “Proper use of TAXUS Express 2 stents” dated April 20, 2007 (PFSB/ELD Notification No. 0420003 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and PFSB/SD Notification No. 0420001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW); “Advices on revision of the package insert for drug-eluting coronary stent” dated February 27, 2008 (PFSB/SD Notification No. 0227001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW); and “Advices on revision of the package insert for drug-eluting coronary stent” dated February 27, 2008 (PFSB/SD Notification No. 0227002 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW).

1. In the “WARNINGS” section of the package insert of the respective drug-eluting coronary stent or drug-coated balloon dilatation catheter for coronary angioplasty, the description presented in the Appendix should be revised.

2. In the “Serious Adverse Events” listed in the “Malfunctions and Adverse Events” section of the “PRECAUTIONS” in the package insert of the respective drug-eluting coronary stent or drug-coated balloon dilatation catheter for coronary angioplasty, the following event should be included:

   Interstitial pneumonia

3. The revised package insert as advised in the abovementioned items 1 and 2 should be uploaded on the Information Services on the website of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”).

4. The respective Marketing Authorization Holders should report to the Medical Device Safety Division, Office of Safety I, PMDA within one month from the date of this notification regarding the actions taken for abovementioned items 1, 2, and 3[Note 1)] in addition to the information provided in the revised package insert to the medical institutions, etc. [Note 2)].

   Note 1) The date scheduled for the start of manufacturing or importing of the product that encloses the revised package insert.

The date or the scheduled date of the release on the Information Services on the website of PMDA.

Note 2) The date of start and the scheduled date of completion of information provision.

5. For any drug-eluting coronary stent or drug-coated balloon dilatation catheter for coronary angioplasty under application for approval, the applicant should report to the PMDA that the revision will be made in the respective package insert (draft).

(Supplement)
Abbott Vascular Japan Co., Ltd.
Johnson & Johnson K.K.
Terumo Corporation
Nipro Corporation
Medtronic Japan Co., Ltd.
Boston Scientific Japan K.K.

(Appendix)

On revision of the “PRECAUTIONS” in the package insert, refer to Table 1 for drug-eluting coronary stents and refer to Table 2 for drug-coated balloon dilatation catheters for coronary angioplasty.

Table 1

Conventional description (Description to be deleted is lined through.)	Revised description (Description to be added is underlined.)
WARNINGS	WARNINGS
• ~~Long-term prognosis for the period exceeding 1 year after the stent placement has not been sufficiently observed in the Japanese clinical settings at this point. Compared to a non-drug coated bare metal stent, this product requires a longer administration period of clopidogrel sulfate or ticlopidine hydrochloride products as antiplatelet therapy following the stent placement. Use of this stent with clopidogrel sulfate or ticlopidine hydrochloride products increases risks of haemorrhage and serious adverse reactions. Therefore, physicians should be encouraged to carefully select appropriate patients before using this stent by balancing risks and benefits for each patient. In the selection of patients, the location of the target lesion (blood vessel), the reference vessel diameter, lesion length and its characteristics, and the size of the myocardial area exposed to the risk of acute or subacute thrombosis should be considered.~~	(Deleted)
• ~~Before use of this product, physicians should adequately advise the patients of the risks associated with the antiplatelet therapy following the stent placement as well as the characteristics of the stent (risks and benefit) and ensure that the patient is fully aware of the information given before using. Physicians should adequately instruct the patients to contact the physician if ischaemic symptoms such as chest pain appear after the stent placement. In~~	(Deleted)

~~particular, physicians should inform the patient of the possible occurrence of life-threatening serious adverse reactions associated with the administration of ticlopidine hydrochloride products, and give the following instructions. The same instructions should be provided when using clopidogrel sulfate.~~	
~~1) In principle, the patient should consult the physician once every 2 weeks since periodical blood tests is required for the first 2 months after the initiation of administration.~~	(Deleted)
~~2) The patient should contact the physician, etc. immediately if symptoms that suggest any adverse reactions occur.~~	(Deleted)
~~• In using this product, appropriate antiplatelet and anticoagulant therapy as well as periodical follow-up after the stent placement should be conducted. For antiplatelet therapy, in particular, the following issues should be noted:~~	(Deleted)
1) Adequately premedicate the patient beforehand so that complete effect will be achieved at the time of stent placement.	• <u>For antiplatelet therapy,</u> adequately premedicate the patient beforehand so that complete effect will be achieved at the time of stent placement<u>.</u>
~~2) It is recommended to administer aspirin indefinitely and clopidogrel sulfate or ticlopidine hydrochloride for at least xx month(s) after the stent placement. Whether administration of the drug should be prolonged or not is determined by the conditions of the patient in consideration of risks of adverse reactions such as haemorrhage, since there have been reports on late stent thrombosis more than 1 year after stent placement.~~	(Deleted)
~~3) In patients treated with antiplatelet therapy for shorter than xx month(s), safety of this product has not been demonstrated. In addition, the frequency and the time of occurrence of thrombosis after administration of clopidogrel sulfate or ticlopidine hydrochloride have not been~~	(Deleted)

~~confirmed in the Japanese patients using this product by a large-scale clinical study.~~	
~~4) Because antiplatelet therapy and/or anticoagulant therapy after stent placement may induce haemorrhage and/or haematoma, patients should contact the physician if they notice abnormal haemorrhage. In addition, they should be advised to inform their physician of their current use of antiplatelet drug when they consult other institution or department.~~	(Deleted)
~~• Be sure to read the package insert of the antiplatelet drug to be used concomitantly.~~	(Deleted)
~~In addition, clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder may occur following administration of ticlopidine hydrochloride products. These symptoms have been reported to occur most commonly within 2 months after the initiation of administration, leading to death in some cases. Therefore, 2-week doses should be prescribed at a time for 2 months after initiating administration as a rule, and the issues listed below should be fully noted. The same issues should be noted when using clopidogrel sulfate:~~	(Deleted)
~~a For 2 months after initiating administration, physicians should be particularly alerted to the emergence of initial symptoms of the abovementioned adverse reactions. In principle, blood count (including differential leukocyte count) and hepatic function tests should be performed once every 2 weeks. If these adverse reactions are observed, administration should be discontinued and appropriate measures should be adopted. Physicians should conduct periodical blood test during the treatment period of the product~~	(Deleted)

~~and be alerted to these adverse reactions.~~ ~~b If thrombotic thrombocytopenic purpura, granulocytopenia, liver disorder etc. are suspected from the conditions of the patient during the administration of the products, physicians should conduct haemogram or liver function test as necessary and take appropriate measures.~~	(Deleted)
• Conduct the coronary stent replacement only at the medical institutions where coronary artery bypass grafting can be expeditiously operated in case a life-threatening complication may occur.	(Same as on the left)
(No relevant description)	• Dual antiplatelet therapy (DAPT) is recommended by the clinical studies for at least xx month(s) after the operation (refer to the section of "CLINICAL STUDY RESULTS") Note 1). Periodical follow-up should be performed as required by the patient conditions and whether the administration of the antiplatelet drug should be prolonged or not is determined in full consideration of the risks of adverse reactions such as haemorrhage as well as the background factors of the patient and the anatomical features of the lesion because there have been reports on late stent thrombosis, a critical malfunction, more than 1 year after stent replacement. Meanwhile, it should be noted that the concomitant use of an antiplatelet drug or an anticoagulant drug may lead to a greater risk of haemorrhage. Note 1) Describe the rationale for the recommended period in the "CLINICAL STUDY RESULTS" section.
(No relevant description)	• Because the use of this product requires the long-term administration of an antiplatelet drug after stent replacement, be sure to read the package insert of the antiplatelet drug to be concomitantly used, and

	take into full consideration the possibility of greater risks of clinically significant adverse reactions such as haemorrhage, thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder. Prior to using this product, it should be ensured that the patient is completely informed of and understands the profiles (risks and benefits) of this product as well as the risks associated with antiplatelet therapy after stent replacement.

Table 2

Conventional description (Description to be deleted is lined through.)	Revised description (Description to be added is underlined.)
WARNINGS	WARNINGS
~~○ Before use of this product, physicians should adequately advise the patient of the risks associated with antiplatelet therapy following the catheter placement as well as the characteristics of the catheter (risks and benefits) and ensure that the patient is fully aware of the information given before using. Physicians should adequately instruct the patients to contact the physician if ischaemic symptoms such as chest pain appear after the treatment. In particular, physicians should inform the patient of the possible occurrence of life-threatening serious adverse reactions associated with the administration of ticlopidine hydrochloride products, and give the following instructions. The same instructions should be provided when using clopidogrel sulfate.~~	(Deleted)
~~• In principle, the patients should consult the physician once every 2 weeks, since periodical blood tests are required for the first 2 months after the initiation of administration.~~	(Deleted)
~~• The patients should contact the physician, etc. immediately if symptoms that suggest any adverse reactions occur.~~	(Deleted)

~~○ After use of this product, appropriate antiplatelet and anticoagulant therapy as well as periodical follow up after the catheter placement should be conducted. For antiplatelet therapy, in particular, the following issues should be noted:~~	(Deleted)
• Adequately premedicate the patient beforehand so that complete effect will be achieved at the time of product use.	• For antiplatelet therapy, adequately premedicate the patient beforehand so that complete effect will be achieved at the time of product use.
~~• Patients treated with this product are recommended to receive dual antiplatelet therapy (DAPT) using aspirin and clopidogrel sulfate or ticlopidine hydrochloride for at least xx month(s) after the operation. After the recommended period, DAPT should be performed adequately after confirmation of the period recommended by the stent placement. Whether administration of the drugs should be prolonged or not is determined by the conditions of the patient in consideration of risks of adverse reactions such as haemorrhage.~~	(Deleted)
~~• In patients treated with antiplatelet therapy for shorter than xx month(s), safety of this product has not been demonstrated.~~	(Deleted)
~~• Because antiplatelet therapy and/or anticoagulant therapy after use of this product may induce haemorrhage and/or haematoma, patients should contact the physician if they notice abnormal haemorrhage. In addition, they should be advised to inform their physician of their current use of antiplatelet drug when they consult other institution or department.~~	(Deleted)
~~• Be sure to read the package insert of the antiplatelet drug to be used concomitantly. In addition, clinically significant adverse reactions such as thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder may occur following administration of ticlopidine hydrochloride products.~~	(Deleted)

~~These symptoms have been reported to occur most commonly within 2 months after the initiation of administration, leading to death in some cases. Therefore, 2-week doses should be prescribed at a time for 2 months after initiation of administration as a rule, and the issues listed below should be fully noted. The same issues should be noted when using clopidogrel sulfate:~~	
~~1) For 2 months after the start of administration, physicians should be particularly alerted to the emergence of initial symptoms of the abovementioned adverse reactions. in principle, blood count (including differential leukocyte count) and hepatic function tests should be performed once every 2 weeks. If these adverse reactions are observed, administration should be discontinued and appropriate measures should be adopted. Physicians should conduct periodical blood tests during the treatment period of the product and be alerted to these adverse reactions.~~	(Deleted)
~~2) If thrombotic thrombocytopenic purpura, granulocytopenia, liver disorder, etc. are suspected from the conditions of the patient during the administration of the products, physicians should conduct haemogram or liver function test as necessary and take appropriate measures.~~	(Deleted)
○ Conduct the operation only at the medical institutions where coronary artery bypass grafting (hereinafter called “CABG”) can be expeditiously operated in case a life-threatening malfunction or adverse event may occur.	(Same as on the left)
(No relevant description)	• <u>Dual antiplatelet therapy (DAPT) is recommended by the clinical studies for at least xx month(s) after the operation (refer to the section of “CLINICAL STUDY</u>

	RESULTS") Note 2). After the recommended period, DAPT should be adequately performed after confirmation of the period recommended by the stent placement. Periodical follow-up should be performed as required by the patient conditions and whether the administration of the antiplatelet drug should be prolonged or not is determined with complete consideration of the risks of adverse reactions such as haemorrhage as well as the background factors of the patient and the anatomical features of the lesion. Meanwhile, it should be noted that the concomitant use of an antiplatelet drug and an anticoagulant drug may lead to a greater risk of haemorrhage. Note 2) Describe the rationale for the recommended period in the "CLINICAL STUDY RESULTS" section.
(No relevant description)	• Because the use of this product requires the administration of an antiplatelet drug after the treatment, be sure to read the package insert of the antiplatelet drug to be concomitantly used and take into complete consideration the possibility of greater risks of clinically significant adverse reactions such as haemorrhage, thrombotic thrombocytopenic purpura (TTP), agranulocytosis, and serious liver disorder. Prior to using this product, it should be ensured that the patient is completely informed of and understands the profiles (risks and benefits) of this product as well as the risks associated with antiplatelet therapy after the use of this product.