Pharmaceuticals and Medical Devices Safety Information

No. 218 October 2005

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

[Outline of Information]

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

1

Result of post-marketing safety measures for ticlopidine hydrochloride products with Cypher Stent

(1) Introduction

It has been notified that the proper use of the Cypher Stent[Note 1)] and preventing the onset of serious adverse reactions from the concurrent use of a ticlopidine hydrochloride product to the relevant marketing authorisation holder in order to thoroughly implement necessary safety measures for the proper use of the products in the "Proper use of ticlopidine hydrochloride products with the Cypher Stent (PFSB/ELD Notification No. 0730005 and PFSB/SD Notification No. 0730005 issued on July 30, 2004)", etc, and it has also been notified prefectural governments, relevant academic societies and organizations to implement dissemination of precautionary information on the proper use of the products. [This matter is presented in the Pharmaceuticals and Medical Devices Safety Information No. 205 (September 2004).]

Moreover, in order to ensure patient follow-up after placement of the Cypher Stent in the coronary artery (hereafter, "Cypher Stent placement"), when a patient is transferred from a medical institution where Cypher Stent placement was performed, in order to ensure that information regarding Cypher Stent placement and ticlopidine hydrochloride administration is transmitted to the hospital where the patient is transferred, it was determined that the manufacturers of Cypher Stent are to receive information from healthcare providers relating to the hospital where the Cypher Stent placement patient is transferred, and that they are to provide this information to the marketing authorisation holder of the relevant ticlopidine hydrochloride products. The marketing authorisation holders of the ticlopidine hydrochloride products are to then implement necessary safety measures to ensure the proper use of the ticlopidine hydrochloride products at the medical institution where the patient has been transferred. Notification of these procedures was transmitted through the "Request for cooperation regarding safety measures for ticlopidine hydrochloride products with Cypher Stent (PFSB/SD Notification No. 0114003 issued on January 14, 2005)", etc.

As approximately 1 year has passed since the Cypher Stent was marketed, the circumstances of safety measures conducted until now (as of June 30, 2005) are presented.

Note 1) Coronary drug-eluting stent was marketed by Johnson & Johnson K.K.

(2) Characteristics of the Cypher Stent and ticlopidine hydrochloride products

The Cypher Stent was approved in March 2004 and has been marketed since August 16, 2004.

The Cypher Stent is the first coronary drug-eluting stent in Japan, and compared to conventional coronary stents, it possesses the following characteristics: ① minimizes coronary restenosis through the pharmacological action of the agent coated onto the surface of the coronary stent, ② therapy using the stent can be applied even for small veins (2.5 mm class). Generally, while it is necessary to conduct antiplatelet therapy to prevent blood clotting during stent therapy, the standard period for conducting antiplatelet therapy when using the Cypher Stent has been determined to be 3 months, which is longer than the standard antiplatelet therapy period for conventional coronary stent therapies (about 1 month), and use of a ticlopidine hydrochloride product is particularly recommended.

Moreover, as serious adverse reactions including thrombotic thrombocytopenic purpura (TTP),

agranulocytosis, and serious liver disorder etc. have been known to occur through the use of ticlopidine hydrochloride, MHLW has alerted by including the following content in the Warning section of package inserts to prevent the onset of these serious adverse reactions:

- In principle, ticlopidine hydrochloride product should be prescribed once every 2 weeks during the first 2 months of administration.
- Periodic testing (blood test, hepatic function) should be conducted once every 2 weeks during the first 2 months of administration.

Until now, "Dear Healthcare Professional Letters" relating to the use of ticlopidine hydrochloride products have been issued 2 times (June 30, 1999, and July 23, 2002).

(3) Implementation of safety measures for the Cypher Stent

The circumstances relating to the use of the Cypher Stent from the initial marketing (August 16, 2004) until June 30, 2005 are summarized in Tables 1 to 3.

- The estimated number of Cypher Stents used was approximately 128700, and the number of patients using the stent was estimated to be approximately 85800 assuming that the average number of stents placed per patient was 1.5 stents (**Table 1**).
- Cypher Stents were delivered to 1243 medical institutions. There were 319 medical institutions which provided patient information etc. to the manufacturers of the Cypher Stent (**Table 2**).
- Patient information which the manufacturer of Cypher Stent received from the aforementioned 319 medical institutions amounted to 4696 cases. The information provided to the marketing authorisation holders of ticlopidine hydrochloride products relating to hospitals where patients were transferred corresponded to 354 cases (**Table 3**).

Table 1. Circumstances of Cypher Stent use

Estimated number of Cypher Stents implanted	approx. 128700
Estimated number of Cypher Stent implanted patients[Note)]	approx. 85800

Note) Assuming the average number of stents used per patient was 1.5 stents.

Table 2. Circumstances of cooperation from medical institutions conducting Cypher Stent placement

Number of institutions where the Cypher Stent was delivered	1243
Number of medical institutions which provided patient information to the manufacturer of Cypher Stent	319
Of which, the number of medical institutions which provided the marketing authorisation holder of ticlopidine hydrochloride product via manufacturer of Cypher Stent with information on hospitals where patients were transferred	319

Table 3. Breakdown of all collected cases

Total number of cases for which patient information was collected by the manufacturer of Cypher Stent	4696
The number of cases for which information on hospitals where these patients were transferred was provided to the marketing authorisation holder of ticlopidine hydrochloride and distributors via manufacturer of Cypher Stent	354 (7.5 %)
Cases receiving out-patient treatment at the hospital where Cypher Stent placement was performed (no transfers)	2310 (49.2 %)
Cases hospitalized at the hospital where Cypher Stent placement was performed (no transfers)	764 (16.3 %)
Cases of transfers from whom consent was not obtained	667 (14.2 %)
Others	601 (12.8 %)

(4) Onset circumstances of adverse reactions from ticlopidine hydrochloride products in Cypher Stent placement patients

Serious adverse reactions reported from administration of ticlopidine hydrochloride products in Cypher Stent patients until June 30, 2005 included 38 cases of serious liver disorder (1 fatal case), 29 cases of granulocytopenia (including agranulocytosis) (1 fatal case), 3 cases of TTP, and 24 cases of other reactions (1 fatal case).

Annual changes in the number of reported adverse reactions including serious liver disorder, granulocytopenia, and TTP etc. in all patients administered the original ticlopidine hydrochloride drug are shown in **Table 4**. However, no large difference in onset conditions of adverse reactions before and after the marketing of the Cypher Stent in August 2004 was seen.

Table 4. Changes in the number of reported adverse reactions from the original ticlopidine hydrochloride product (aggregated on day 1 of administration)

	July 2003 - June 2004	July 2004 - June 2005
Liver disorder	85 cases (3 fatal cases)	89 cases (4 fatal cases)
Granulocytopenia	33 cases (5 fatal cases)	46 cases (1 fatal case)
TTP	7 cases (4 fatal cases)	8 cases (no fatal case)
Others	47 cases (no fatal case)	46 cases (3 fatal cases)

Note) Reports include cases evaluated by experts to have a negative causality with the drug.
There may be some duplicated reports among the number of reported cases.

(5) Future safety measures etc.

While the Cypher Stent is superior to conventional stents in terms of reducing the occurrence of restenosis, etc., it is important that it be properly used together with the ticlopidine hydrochloride product concurrently used. It is necessary that the manufacturers etc. of Cypher Stent and ticlopidine hydrochloride products continue to consider necessary safety measures to ensure proper use by medical institutions. It is requested that healthcare providers pay heed to the following points:

① To prevent serious adverse reactions from ticlopidine hydrochloride, the drug should be prescribed once every 2 weeks and periodic testing (blood test, hepatic function) should be conducted once every 2 weeks during the first 2 months of administration.

② Patients administering a ticlopidine hydrochloride product should be instructed not to discontinue administration at their own discretion, subjective symptoms of serious adverse reaction should be explained[Note 2)], and if such symptoms are observed, they should consult their primary physician etc. to receive instruction of proper administration.

③ When adverse reactions from ticlopidine hydrochloride or adverse event of Cypher Stent are observed, healthcare providers should make adverse reaction report in accordance with article 77-4-2-2 of the Pharmaceutical Affairs Law.

Note 2) Main subjective symptoms

a) Pyrexia
b) Sore throat
c) Haemorrhage from nose or gums
d) Haematuria or chromaturia (brown)
e) Birth mark formation (purple, red)
f) Yellow discoloration of skin or eye
g) Eczema
h) Anorexia
i) Consciousness decreased
j) Severe fatiguability

2

Serious skin disorders induced by drugs

(1) Introduction

Skin disorders are commonly known adverse reactions to drugs. As the serious skin disorders, the Stevens-Johnson syndrome (SJS) (oculomucocutaneous syndrome) and toxic epidermal necrolysis (TEN) are identified.

The pathology etc. of SJS and TEN have been described in Pharmaceuticals and Medical Devices Safety Information No. 163 (November 2000 issue), No. 177 (May 2002 issue), and No. 203 (July 2004 issue). It has been also described the circumstances of adverse reactions reported to Ministry of Health, Labour and Welfare (MHLW) from April 1, 1997 to October 26, 2003.

As adverse reaction reports have been collected over an approximately 2 years since the last time, MHLW presents the circumstances etc. for the onset of SJS and TEN reported until September 30, 2005. In addition, information on over the counter drugs is summarized from this bulletin.

(2) Stevens-Johnson syndrome (oculomucocutaneous syndrome), toxic epidermal necrolysis

SJS (oculomucocutaneous syndrome) is synonymous with erythema exsudativum multiforme major (EEMM), and toxic epidermal necrolysis is considered the most severe among the skin disorders[1)].

TEN is also referred to as Lyell syndrome. Disorders that demonstrate similar symptoms include staphylococcal scalded skin syndrome (SSSS) and graft versus host disease (GVHD) after blood transfusions.

The incidence of these disorders is extremely low, consisting of approximately 1 to 6, 0.4 to 1.2 [2, 3)] per year for every 1 million people. After developing these disorders, there are cases of resulted in poor prognosis, and even after skin symptoms have improved, disorders with the eyes and respiratory tract may still remain.

1) Initial symptoms and clinical course

The initial symptoms of SJS are pyrexia and erythema (target lesion, etc.) distributed symmetrically mainly around the back surface of joints, which rapidly increase in the amount. Increase in severity of erythema is resulting in the development and fusion of blisters and erosions. They often accompany enanthema of the eyes, oral mucosa, and vulva, and are demonstrated by increased white blood cell red, increased blood cell sedimentation rate, CRP positive, etc. in test findings. Erythema multiforme exudativum-like skin eruptions (target lesions) and rapid distribution of enanthema over an extensive area occur together with general symptoms such as pyrexia. With complications such as respiratory disorders (pneumonia, etc.) and liver disorder, it has been reported that the mortality rate of SJS is 6.3%[4)].

On the other hand, TEN causes symptoms of pyrexia and erythaema over an extensive area such as the axilla, vulva, and torso, followed by rapid blister formation which can be easily broken (Nikolsky's sign) together with general erosion. These symptoms resemble burns second degree, and pain is significant. Clinical laboratory tests often confirm abnormal blood, liver and electrolyte findings. They are often complicated by multi-organ failure (liver disorder, renal disorder, respiratory disorder, gastrointestinal disorder etc.), and it has been reported that mortality rate is also high, between 20%-30%[4, 5)].

2) Pathogenesis and mechanisms

These disorders are thought to result from infectious diseases caused by various viruses such as the herpes simplex virus and mycoplasma pneumoniae, bacteria or fungi and allergic skin reactions (type III allergy reactions) that occur from drugs, foods, endocrine abnormalities, malignant tumors, physical stimuli, etc. Drugs are often attributed as the cause, and it has been reported in some literature that 59% of SJS cases are estimated to have resulted from drugs[4)] and 90% and more of TEN cases are estimated to have resulted from drugs[4, 5)]. The onset mechanisms of these skin disorders are not yet clear, and it is also extremely difficult to predict the onset of these severe skin disorders before administration of drugs.

3) Causative drugs

There are a wide range of causative drugs mainly including antibiotics, antipyretics, analgesics, and anti-inflammatory agents, antiepileptics, antigout agents, sulfonamides, peptic ulcer agents, hypnotic sedatives/anxiolytics, psychotropics, therapeutic agents for glaucoma, muscle relaxants, and hypertensive agents, it has also been reported that these skin disorders result from the administration of other drugs as well[2, 4-7)].

4) Treatment

If initial symptoms such as pyrexia and rashes are confirmed for drug-induced SJS and TEN, the most important and best treatment is to immediately discontinue administration of the drug suspected to be the cause. However, attention is necessary as there are cases where symptoms increase in severity and develop into SJS and TEN even if administration is discontinued. In general, if SJS and TEN occur, systemic administration of adrenocortical hormone drug or plasma exchange therapy, administration of vitamins, in addition to administration of antibiotics for the purpose of preventing secondary infections is carried out. External antibiotics and external adrenocortical hormone preparations are used on the skin surface. For mucosal surfaces, treatment of apertural area such as gargling and eye washing are performed together with the above[6-8)]. It is recommended that these treatments be performed at a hospital possessing dermatological department inpatient facilities[9, 10)].

(3) Adverse reactions reported to MHLW from October 27, 2003 to September 30, 2005

SJS and TEN induced by drugs reported until October 26, 2003 have been summed and presented in the Pharmaceuticals and Medical Devices Safety Information No. 203. This time, MHLW has summarized adverse reactions reported from October 27, 2003 to September 30, 2005.

Among adverse reactions reported by marketing authorisation holders during this period (including reports assessed by experts to have a negative causality with drugs), 905 cases of adverse reactions of SJS or TEN were reported [1.7% of all 53576 adverse reactions reported during this period]. Of these, reports of over the counter drugs included among the suspected drugs amounted to 61 cases (6.7% of adverse reactions of SJS or TEN reported during this period).

As for the outcomes of the 905 reports of SJS or TEN adverse reactions, 535(59.1%) recovered or improved, 56(6.2%) did not recover, 36(4.0%) had sequelae, 95(10.5%) died, and outcome etc. was unknown in 183(20.2%). When these figures are compared to the reports collected over an approximately 2 and a half year period from April 1, 2001 to October 26, 2003 which were presented in the Pharmaceuticals and Medical Devices Safety Information No. 203, a large divergence was not seen in terms of number of reports and outcomes (**Table 1**). As for the number of reports, pay adequate attention to the fact that there may be duplications of reporting and that cases judged by experts to have a negative causality with drugs are included.

Drugs which were reported to be suspected drugs for the onset of SJS and TEN amounted to 273 active ingredients, and the most numerous reports according to drug and therapeutic category are shown in **Tables 2** and **3**. With regard to the order of report numbers, please note that it is not possible to make simple comparisons as the sales volumes for each drug, methods of use, frequency of use, concomitant

drugs, primary diseases, complications, etc. differ depending on the case.

Table 1. Number of adverse reactions reported as SJS and TEN and their outcomes (including reports assessed by experts to have a negative causality with drugs)

Period	Category	Number of adverse reactions reported as SJS or TEN (ratio of overall adverse reaction reports)	Outcome of cases of adverse reactions reported as SJS or TEN: Number of reports (ratios among SJS or TEN adverse reaction reports) [number of reports per annum]				
			Recovered or improved	Not recovered	Sequelae	Death	Outcome unknown etc.
October 27, 2003 | September 30, 2005	All drugs (including OTC drugs)	905 (1.7%) [472.2 reports/year]	535 (59.1%) [279.1 reports/year]	56 (6.2%) [29.2 reports/year]	36 (4.0%) [18.8 reports/year]	95 (10.5%) [49.6 reports/year]	183 (20.2%) [95.5 reports/year]
	OTC drugs only	61	40 (65.6%)	2 (3.3%)	3 (4.9%)	4 (6.6%)	12 (19.7%)
April 1, 2001 Note 1 | October 26, 2003	All drugs (including OTC drugs)	1064 (1.5%) [411.9 reports/year]	702 (66.0%) [271.7 reports/year]	66 (6.2%) [25.5 reports/year]	62 (5.8%) [24.0 reports/year]	106 (10.0%) [41.0 reports/year]	128 (12.0% [49.5 reports/year]
	OTC drugs only	58	-- Note 2	--	--	--	--

Note 1: Refer to the Pharmaceuticals and Medical Devices Safety Information No. 203.

Note 2: Until the previous issue of Pharmaceuticals and Medical Devices Safety Information, the cases of reports of adverse reactions induced by OTC drugs are unknown.

Table 2. Most numerously reported suspected drugs (as for each drug)

Name of drug	Number of reported cases
Carbamazepine	37
Allopurinol	36
Diclofenac sodium	28
Acetaminophen	27
Loxoprofen sodium	25
Cefcapene pivoxil hydrochloride	24
Phenytoin	21
Levofloxacin	20
Salicylamide/acetaminophen/ anhydrous caffeine/ promethazine methylenedisalicylate	19
Phenobarbital	18

Table 3. Most numerously reported suspected drugs (according to therapeutic category)

	Therapeutic Category	Number of reported cases
All drugs (including OTC drugs)	Antibiotics	160
	Antipyretics and analgesics, anti-inflammatory agents	135
	Antiepileptics	86
	Combination cold remedy	57
	Synthetic antibacterials	40
	Antigout agents	37
	Peptic ulcer agents	34
OTC drugs only	Combination cold remedy	36
	Antipyretics and analgesics, anti-inflammatory agents	15
	Otological agents	2
	Kampo medicines	2

(4) Conclusion

Although the incidences of SJS and TEN are rare, once they occur, there are cases of fatal outcomes from complications of multi-organ failure, etc. As well, SJS and TEN are serious skin disorders where disorders in the eyes and respiratory tract, etc. remain even if skin symptoms improve. These skin disorders, although rare, have the potential of occurring irrespective of the drug administered.

If rash etc. accompanying hyperthermia is observed after drug administration, administration of the suspect drug should be discontinued, and if the onset of SJS or TEN is suspected, it is important that the patient promptly be referred to a dermatologist. For this reason, when a healthcare provider administers or sells a drug which has been numerously reported such as antibiotics, antipyretics, analgesics, anti-inflammatory agents, antiepileptics, combination cold remedy, synthetic antibacterials, and antigout agents etc., they should provide explanations to patients regarding initial symptoms of these adverse reactions, and instruct patients to seek immediate medical assessment when these symptoms are observed.

Presently, MHLW is drafting the “Manual for serious adverse reactions by disease” in association with related societies etc. which is a comprehensive compilation of initial symptoms, typical cases, and diagnostic methods etc. of adverse reaction for the purpose of contributing to the early identification and prompt manage to adverse reactions. MHLW is also planning to include information relating to SJS and TEN.

<References>

1) Assier, H., et al.: Erythema Multiforme With Mucous Membrane Involvement and Stevens-Johnson Syndrome Are Clinically Different Disorders With Distinct Causes, Arch. Dermatol., 131: 539-543 (1995)
2) Roujeau, J-C., et al.: Medication Use and The Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, N. Engl. J. Med., 333: 1600-1607 (1995)
3) Rzany, B., et al.: Epidemiology of Erythema Exsudativum Multiforme Majus, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis in Germany (1990-1992): Structure and Results of a Population Based Registry, J. Clin. Epidemiol., 49: 769-773 (1996)
4) Michiko Aihara, Zenro Ikezawa: “Clinical investigation of deaths from Toxic Epidermal Necrolysis in Japan: comparative investigation of cases of TEN survival and Stevens-Johnson syndrome (SJS) deaths.” The Journal of Dermatology, 109 (11): 1581-1590 (1999) (In Japanese)
5) Hiroko Nanko: “Clinical Analysis of 126 Cases of Toxic Epidermal Necrolysis in Japan: Whether Differentiation from Post-transfusion GVHD is possible.” 45: 571-578 (1991) (In Japanese)
6) Ryuichi Takahashi ed.: “Clinically Significant Adverse Drug Reactions Made Easy as Written by a Clinician That Patients Become Aware Of.” Elsevier Japan (1998) (In Japanese)
7) Seiichi Izaki: “TEN (Toxic Epidermal Necrolysis)” Kawagoe Clinical Conference, KCC Series, No. 39 (1998) (In Japanese)
8) Shigeo Ikeda, et al., ed.: Standard Dermatology 5th Edition, Igaku-Shoin Ltd. (1997) (In Japanese)
9) Tetsuo Shiohara: Diagnosis and Therapy, 87 (Suppl): 37-41 (1999) (In Japanese)
10) Shotaro Harada, et al.: Journal of Clinical Therapeutics and Medicine, 17 (9): 1261-1273 (2001) (In Japanese)

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List of products subject to Early Post-marketing Phase Vigilance

(As of October 1, 2005)

Nonproprietary name Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Oxaliplatin Elplat for Injection 100 mg	Yakult Honsha Co., Ltd.	April 6, 2005
Tacrolimus Hydrate Prograf Capsules 0.5 mg and 1 mg*[1]	Astellas Pharma Inc.	April 11, 2005
Emtricitabine Emtriva Capsules 200 mg	Japan Tobacco Inc.	April 19, 2005
Emtricitabine/Tenofovir Disoproxil Fumarate Truvada Tablets	Japan Tobacco Inc.	April 19, 2005
Rosuvastatin Calcium Crestor Tablets 2.5 mg and 5 mg	AstraZeneca K.K.	April 27, 2005
Bosentan Hydrate Tracleer Tablets 62.5 mg	Actelion Pharmaceuticals Japan Ltd.	June 10, 2005
Tamibarotene Amnolake Tablets 2 mg	Toko Pharmaceutical Industrial Co., Ltd.	June 13, 2005
Tocilizumab (Genetical recombination) Actemra for Intravenous Infusion 200	Chugai Pharmaceutical Co., Ltd.	June 13, 2005
Adenosine Adenoscan Injection 60 mg	Daiichi Suntory Pharma Co., Ltd.	June 21, 2005
Voriconazole Vfend Tablets 50 mg and 200 mg, Vfend 200 mg for Intravenous Use	Pfizer Japan Inc.	June 27, 2005
Luliconazole Lulicon Cream 1 %, Lulicon Solution 1%	Pola Chemical Industries, Inc.	July 20, 2005
Fludeoxyglucose FDGscan Injectable	Nihon Medi-Physics Co., Ltd.	August 1, 2005
Fludeoxyglucose FDGscan-MP Injectable	The Medical and Pharmacological Research Center Foundation	August 1, 2005
Monteplase (Genetical recombination) Cleactor Injection 400000, 800000, and 1600000[*2]	Eisai Co., Ltd.	August 5, 2005
Follitropin Beta (Genetical recombination) Follistim Inj. 75 and 150	Nippon Organon K.K.	August 11, 2005
Doripenem Hydrate Finibax 0.25 g IV Solution	Shionogi & Co., Ltd.	September 16, 2005
Dehydrated Ethanol Anhydrous Ethanol Injection “Fuso”	Fuso Pharmaceutical Industries, Ltd.	September 16, 2005
Dehydrated Ethanol Dehydrated Ethanol Inj. “Merck”	Merck Hoei Ltd.	September 20, 2005

Pilocarpine Hydrochloride Salagen Tab. 5 mg	Kissei Pharmaceutical Co., Ltd.	September 22, 2005
Gemtuzumab Ozogamicin (Genetical recombination) Mylotarg Injection 5 mg	Wyeth K.K.	September 22, 2005

Note) Subject to additional indication etc.

*1: An additional indication for “Rheumatoid arthritis (only for cases which are not adequately responsive to conventional therapies”

*2: An additional indication for “lysis of pulmonary thrombosis of acute pulmonary embolism accompanied with unstable homodynamic”