Pharmaceuticals and Medical Devices Safety Information

No. 200 April 2004

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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).

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

[Outline of Information]

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

1

Prevention of overdose by use of OptiPen Pro-1 (insulin self-injection device)

1. Introduction

This manual insulin self-injection device has been marketed since December 12, 2003. To date more than 50000 pens have been distributed for use with insulin glargine (genetical recombination) (brand name: LANTUS Inj. Cart 300). Among these products, there have been reports of excessive discharge of insulin when priming. In response to the reports, the manufacture conducted the investigation and as the result, they confirmed excessive discharges of insulin when removing the insulin cartridge from the device during use, or when a position of piston bar inadvertently displaced at the replacement of insulin cartridge. Therefore, MHLW issued the Dear Healthcare Professional Letters and inform the details of the reports to alert healthcare professionals to the risks again.

2. Dear Healthcare Professional Letters

(1) Background

According to the reports collected from December 12, 2003 (date of marketing) to March 4, 2004, there have been 7 cases of excessive discharge of insulin when priming the pen in Japan (There was no patient actually injected). As for the foreign reports collected from September 2003 to March 4, 2004, there have been 3 cases of hypoglycaemia, which were suspected to be caused by overdose of insulin following the use of this product. In response to these adverse event reports, MHLW currently decided to introduce the contents of these reports to medical institutions and healthcare professionals in the light of the results of investigation conducted by the manufactures.

(2) Case reports

Table 1 gives the summaries of 7 cases among all cases reported in Japan.

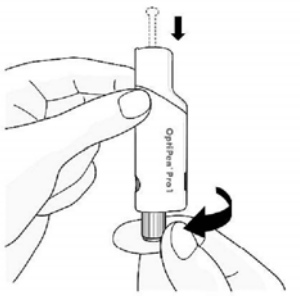
Table 1 Case Summary

No.	Health hazard	Result of performance inspection of this product	Details of report from medical institution
1	No	Normal	When the nurse dialed the dosage knob before giving injection of insulin glargine (genetical recombination) (brand name: LANTUS Inj. Cart 300), she could not dial past 3 units. When the person in pharmacy priming the device by dialing the dosage knob at a dose of 2 units, 2 units and more of insulin were discharged (Comment from patient: Approximately 20 units of insulin were discharged from the remaining 40 units). The device worked properly after replacing the cartridge. However, a new device was given to the patient by way of caution.
2	No	Normal	When the nurse primed the device of a hospitalized patient (2 units), approximately 10 units and more of insulin (confirmed visually) were discharged from the needle tip. The diabetes mellitus specialist checked the device with the nurse the next day, 10 units and more of insulin were discharged from the needle tip when priming. The priming from the second and subsequent occasions was normal and the selected dose was apparently discharged. At the present, the priming is repeated two times in some cases as a precautionary measure.
3	No	Normal	The piston bar could not be displaced when replacing an insulin cartridge. More than selected units were discharged at the trial injection (2 units) conducted after loading the cartridge. In the course of repeating the procedure, even the dosage knob could not be dialed (running idle). No particular problem has been reported after replacing the product on the same day. As far as the pharmacist remembers, the piston bar was not in the correct position when replacing the insulin cartridge.
4	No	Normal	The patient reported that more than 2 units were discharged when priming with 2 units immediately after replacing the cartridge. When the medical representative inspected the device, it worked properly.
5	No	Normal	A click of the dosage knob was lost. After that, more than dialed amount of insulin was discharged.
6	No	Normal	The patient told the nurse that he/she could not know whether the priming was properly done because the knob made no sound in spite of turning the dial. Although the person in the department of pharmacy tried the priming with 2 units, the injection button could be pressed much more than adjusted unit in many times.
7	No	Normal	More than dialed number of insulin was discharged when priming.

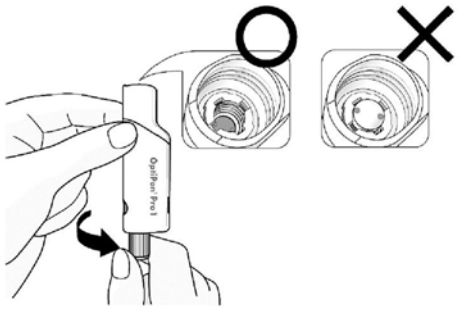
(3) Cautions to users

1) Do not remove insulin cartridge from the body of pen during use. If the cartridge is removed, do not use the removed cartridge again. [The position of the piston bar is displaced and overdose would be caused.]

2) When replacing an insulin cartridge, hold the device facing upward as shown in Figure 1 below, then pull the piston bar to return to the bottom of position shown in Figure 2. (Do not push it back with fingers, etc.) [A space between rubber piston and piston bar cannot be secure and overdose would be caused.]



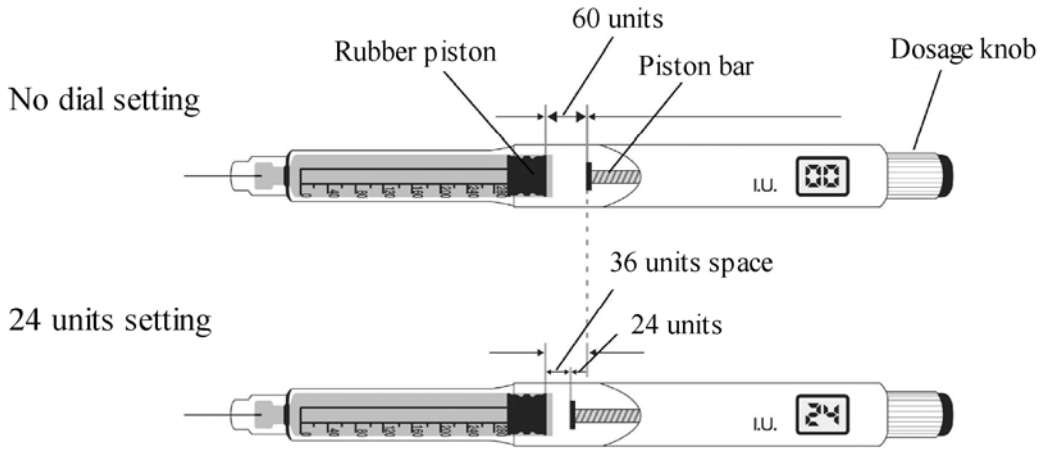
(Figure 1)



(Figure 2)

3) Always prime immediately before each injection as well as after replacing a cartridge. [In order to prevent overdose regarding 1) and 2), as well as removing bubbles, which is a primary object of priming]

This product has approximately 8 mm space (corresponds to 60 units) usually existing between the rubber piston and the insulin expelling piston bar. On administration, after adjusting the dial of units need to be injected, the piston bar moves forward for the dialed dose. After the piston bar moves forward for 60 units at an injection, the rubber piston is pushed forward for the length of dialed dose and insulin is came out (In case where the piston bar and the rubber piston are closely touched resulting from an operational error, a maximum of 60 units of insulin are discharged).



Displacement of the piston bar to the rubber piston side by failure to follow the instructions 1), 2), and 3) in the “Cautions to users” may result in discharge of excessive insulin (60 units at the maximum) at the next injection.

(4) Request to medical institution

On March 5, 2004 “Dear Healthcare Professional Letter” regarding prevention of overdose following the use of this product were distributed. The letters were issued to promote understanding proper use of this insulin self-injection device in response to the 7 cases of excessive discharge of insulin when priming that were reported in December 2003 and after in Japan.
The product must be properly used to prevent overdose of insulin and a risk of hypoglycaemia. Healthcare professionals should advise all patients who are prescribed this product of operating precautions when using this product.

2

Crude drugs and drug products with possible adverse reaction when mistakenly imported due to the similarity in names

(1) Summary

Aristolochic acid, contained in the family Aristolochiaceae, may cause renal disorders. Although MHLW has already alerted healthcare professional about the risk in Pharmaceuticals and Medical Devices Safety Information No. 161 (July 2000 issue), the cases of renal disorders (aristolochic acid nephropathy, CHN: Chinese herb nephropathy, in foreign countries) caused by aristolochic acid are continuously reported in Japan and foreign countries. These cases were caused by traditional medicines (traditional chinese medicines or traditional Chinese medicinal products in China and Taiwan) brought in Japan from China or Taiwan for personal use, decoction, and health foods such as healthy tea similar to these medicines. The crude drugs and Kampo products approved as a drug in Japan do not contain aristolochic acid.

Recently, it has been reported that a crude drug named Guangfangji (written as "广防己" in modern simplified Chinese character) containing aristolochic acid were mistakenly imported to Japan as Hanfangji and used in Japan as Sinomenium Stem (JP) resulting in aristolochic acid nephropathy probably associated with the drug. It is assumed that such mix-up may be likely to occur due to the similarities in the forms and the names between the two crude drugs. Therefore, although drugs approved in Japan (crude drugs and Kampo products) would not be a concern, the drug products with crude drugs possibly contain aristolochic acid may be bought and taken by purchase abroad or personal import over the Internet. This section presents precautions for the crude drugs used in China and other countries with the possible risks of adverse reaction following misuse due to the similarity in names for reference.

"Kampo medicines" generally used in Japan refers to drugs combined of crude drugs, which are prepared by uniform criteria in conformity with the treatment of Kampo medicine that is established in Japan. The quality and specification of such drugs are different from those of "traditional medicines (traditional Chinese medicines or traditional Chinese medicinal products)" marketed in China, etc. The following "Kampo products" refer to "Kampo medicines" generally used in Japan approved as a drug (OTC drug and ethical drug).

(2) Crude drugs with caution

1) Akebia Stem (Mutong 木通)

"Mutong distributed as a crude drug" and "Mutong used as a raw material in Kampo products" in Japan refer to Akebia Stem listed in the Japanese Pharmacopoeia. The source plant of such drugs is climbing stems of *Akebia quinata* Decaisne and *Akebia trifoliata* Koidzumi (*Lardizabalaceae*) that does not contain aristolochic acid. However, caution should be exercised because nephrotoxic Guanmutong could be used instead of Akebia Stem in China due to potent efficacy such as diuretic effects of the plant.

In modern simplified Chinese character, although Guanmutong is described as "关木通", it is also labeled "木通 (Mutong)" in some of Guanmutong. The source plant of Guanmutong is *Aristolochia manshuriensis* Kom., which contains aristolochic acid. In China and other countries, *Aristolochia kaempferi* Willd. (huai tong 淮通) in Aristolochiaceae can also be distributed as Mutong. Therefore, caution should be exercised for a product of China labeled "Mutong".

2) Sinomenium Stem (Fangji 防已)

"Fangji, Hanfangji, and Mufangji distributed as a crude drug" and "Fangji, Hanfangji, and Mufangji used as a raw material in Kampo products" in Japan refer to Sinomenium Stem listed in the Japanese Pharmacopoeia. The source plant of such drugs is climbing stems and rhizomes of *Sinomenium acutum* Rehder et Wilson (*Menispermaceae*) that does not contain aristolochic acid. However, caution should be exercised because Guangfangji (広防己) (*Aristolochia fangchi* Y.C. Wu ex L.D. Chow) containing aristolochic acid could be used in China and other countries due to potent efficacy such as diuretic effects of the plant. In Chinese character, the name of Fenfangji (粉防己) (the source plant is *Stephania tetrandra* S. Moore) is similar to Sinomenium Stem (防已). Although Fenfangji itself is nontoxic, as it does not contain aristolochic acid, there are foreign reports of many renal disorders due to the mix-ups of Fenfangji and Guangfangji. In addition, caution should be exercised for the product labeled "Fangji", as it can be an abbreviation of "Guangfangji" in some cases.

Although the successive biblio of herbal medicines in Japan and China use both "防已 (Boui in Japanese)" and "防己 (Bougi or Bouki in Japanese)", these are defined as "Sinomenium Stem (防已)" in the current Japanese Pharmacopoeia, and "Fangji (Bouki)" in Pharmacopoeia of the People's Republic of China. Therefore, caution should also be exercised for the differences in characters of Japanese and Chinese.

Boui (Fangji) = 防已 ……Japanese
Bouki = 防己 ……Chinaese
(已 and 己 are different characters)

3) Asiasarum Root (Xixin 細辛)

In Japan, underground roots and rhizomes of Xixin are used as a crude drug. But the use of aerial parts of Xixin, which contains nephrotoxic aristolochic acid are prohibited by the Japanese Pharmacopeia Fourteenth Edition. "Xixin as crude drug" and "Xixin used as raw material in Kampo products" distributed in Japan would not be a concern as long as those are Asiasarum Root listed in the Japanese Pharmacopoeia, as it does not contain aristolochic acid. The source plant of Xixin is *Asiasarum heterotropoides* F. Maekawa var. *mandshuricum* F. Maekawa (*Aristolochiaceae*) and *Asiasarum sieboldii* F. Maekawa. Caution should be exercised as the whole plant of Xixin including aerial parts, which possibly contains aristolochic acid is distributed as a crude drug in China and other countries, and can be mixed in Japan.

4) Saussurea Root (Muxiang 木香)

In the Japanese Pharmacopoeia, Muxiang refers to the roots of *Saussurea lappa* Clarke (*Compositae*), which does not contain aristolochic acid. Caution should be exercised as Qingmuxiang (*Aristolochia debilis* Sieb. et Zucc.) and Nanmuxiang (*Aristolochia yunnanensis* Franch.) containing aristolochic acid can be used as Muxiang in China and other countries.

3

Change of URL in response to the establishment of the Pharmaceuticals and Medical Devices Agency

Information on package inserts of drugs, adverse reactions, and approval review, etc. has been provided on the pharmaceuticals information website of the Organization for Pharmaceutical Safety and Research (OPSR). On April 1, 2004, the Pharmaceuticals and Medical Devices Agency was established by merging the OPSR and the parts of the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences and the Japan Association for the Advancement of Medical Equipment. Accordingly, please note that the URLs have changed to the followings. We look forward to your visit to the websites.

Pharmaceuticals and Medical Devices Agency

http://www.pmda.go.jp (In Japanese)

http://www.pmda.go.jp/english/index.html (In English)

PMDInfo Web

http://www.info.pmda.go.jp (In Japanese)

4

Health hazard caused by natural health foods and non-approved drugs

○ **Health hazards caused by natural health foods and non-approved drugs should be reported to a public health center.**

The public health centers in every district in the nation are in charge of receiving complaints and consultation on health hazards caused by natural health foods and non-approved drugs, and conducting necessary examination. Among the received reports, the cases of health hazard are to be reported to Ministry of Health, Labour and Welfare. Therefore, suspicious health hazards caused by the use of natural health foods and non-approved drugs should be immediately informed to a nearby public health center. Prompt accumulation of such information can prevent the spread of health hazards.