Pharmaceuticals and Medical Devices Safety Information

No. 350 February 2018

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 350 February 2018

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications 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, 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

ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAL	Bronchial lavage
CK (CPK)	Creatine kinase (Creatine phosphokinase)
CRP	C-reactive protein
CT	Computed tomography
ED	Erectile dysfunction
EPPV	Early Post-marketing Phase Vigilance
ER	Emergency room
FDA	Food and Drug Administration
FiO2	Fraction of inspiratory oxygen
FY	Fiscal year
Hb	Hemoglobin
ICU	Intensive care unit
IgM	Immunoglobulin M
JCS	Japan Coma Scale
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
NIHS	National Institute of Health Sciences
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SP-D	Surfactant protein D
SpO2	Oxygen saturation
WHO	World Health Organization

1

An Incident of Distribution of Counterfeit HARVONI Combination Tablets and Government Measures Against Counterfeit Drugs

In January 2017, it turned out that counterfeit hepatitis C drug, “HARVONI Combination Tablets,” were distributed by some wholesalers in Japan. The product was dispensed by a pharmacy and reached a patient. Fortunately, no patients actually took the counterfeit drugs distributed in the incident after all and no adverse health effects occurred, but the incident was perceived as a great shock in Japan where distribution of counterfeit drugs was inconceivable unless privately imported as the general sentiment.

Needless to say, it is extremely important to ensure quality control of drugs during distribution, including intercepting counterfeit products, in order to gain the trust of citizens in drugs as products related to their lives.

Responding to this incident, the Ministry of Health, Labour and Welfare (MHLW), set up an expert review committee to investigate proper measures against distribution of counterfeit prescription drugs, and through the discussions in the committee, obligations that the government, marketing authorization holders (MAHs), drug wholesalers, pharmacies, and medical institutions should fulfill were formulated into a report in December 2017.

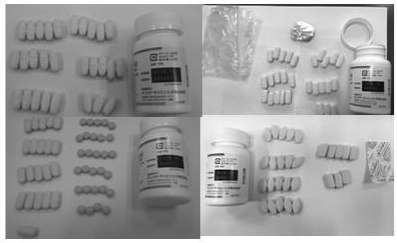
This section hereby introduces the overview of the counterfeit HARVONI distribution incident and the outline of the report prepared by the expert review committee. In addition, the government activities to prevent distribution of counterfeit drugs in Japan through private import are also introduced.

Summary of incident: Distribution of counterfeit HARVONI Combination Tablets

- In January 2017, it turned out that counterfeit hepatitis C drug, HARVONI Combination Tablets, were distributed. The products were dispensed by a pharmacy run by a pharmacy franchise in Nara.
- Five bottles of counterfeit products were found in franchise pharmacies in Nara and 10 bottles in multiple wholesalers in Tokyo.
- The patient who was dispensed counterfeit tablets noticed the differences and did not take them.

○ Authentic HARVONI Combination Tablets

○ Counterfeit HARVONI Combination Tablets, which were found in franchise pharmacies in Nara

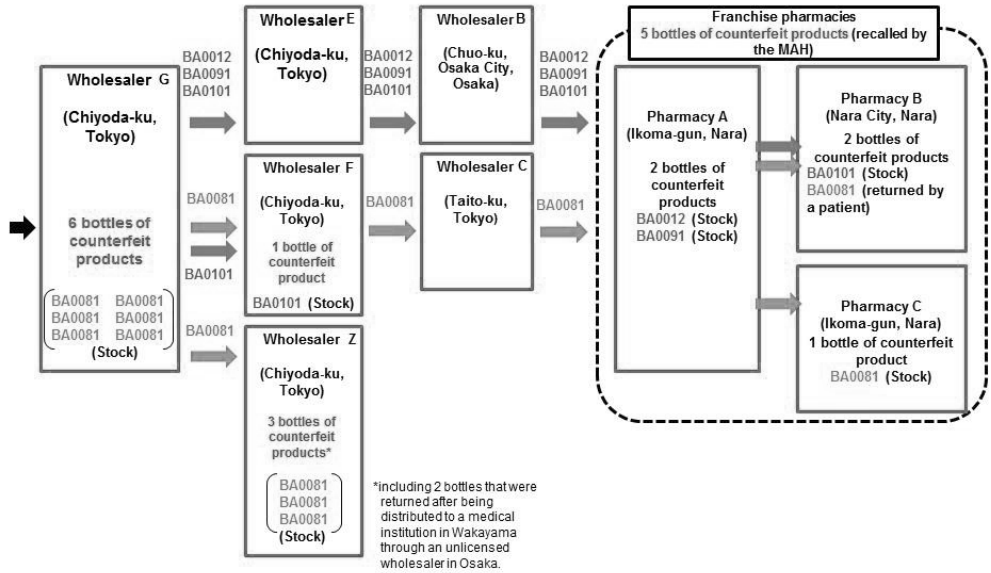


1. An Incident of distribution of counterfeit hepatitis C drug HARVONI Combination Tablets

In January 2017, distribution of counterfeit products was uncovered when a patient noticed something strange in the HARVONI Combination Tablets the patient had received in a pharmacy in Nara and consulted with a pharmacist. Subsequent analyses revealed the counterfeit product contained vitamin preparations, herbal extract preparations, and other hepatitis C drugs marketed in Japan. The patient, who had been treated with authentic HARVONI Combination Tablets, was able to notice the difference in the dispensed counterfeit drug and did not take it.

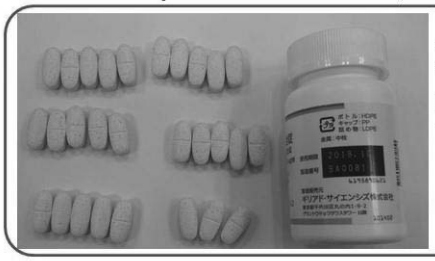
Responding to the report of detected counterfeit drugs, regulatory authorities of the central and local governments conducted on-site inspections of related pharmacies and wholesalers, obtained purchase slips and other documents, investigated the distribution route, and found 5 bottles of counterfeit products in some franchise pharmacies in Nara and 10 bottles of counterfeit products in multiple wholesalers in Tokyo. They found these counterfeit products had been taken out of the "sealed box" which should have housed authentic HARVONI Combination Tablets and were distributed after being sold to a certain so-called "cash-only wholesaler" in Tokyo by an unidentified person under a false name.

Summary of incident: Distribution of counterfeit HARVONI Combination Tablets



Results of analyses of counterfeit products (Excerpts)

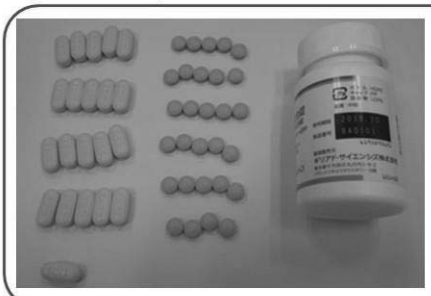
Counterfeit product found in Nara, Case 1 (Lot No.: BA0081) × 2 bottles



28 yellow, spotted tablets were contained in the bottle, in different shapes from HARVONI Combination Tablets.

Detected compounds: multiple vitamins
→ The tablets were presumed to include multiple vitamins.

Counterfeit product found in Nara, Case 2 (Lot No.: BA0101)



21 light purple in an appearance similar to SOVALDI Tablets and 29 light purple tablets were mixed in the bottle.

- **Tablets which appeared similar to SOVALDI Tablets**
  Detected compound: sofosbuvir (active ingredient of SOVALDI Tablets)
  →The tablets were assumed to be SOVALDI Tablets 400 mg.
- **Light purple tablets**
  Detected compounds: albiflorin, paeoniflorin (ingredient of peony), liquiritin, glycyrrhizin (ingredient of licorice), ephedrine, pseudoephedrine (ingredient of ephedra), schizandrin, gomisin A (ingredient of schisandra fruit), asarinin (ingredient of asiasarum root), cinnamic acid
  → The tablets were assumed to be Kampo medicines for rhinitis and cold.

2. Government actions responding to distribution of counterfeit hepatitis C drug HARVONI Combination Tablets

MHLW, responding to the report of counterfeit products found in the pharmacies, conducted on-site inspections of pharmacies and wholesalers in collaboration with related local regulatory authorities, seized the counterfeit products, and identified the distribution route as mentioned above.

The ministry also in collaboration with Gilead Sciences, Inc., the MAH of HARVONI Combination Tablets, analyzed ingredients contained in the found counterfeit products, released information on the appearance and other details of the products, and alerted wholesalers and medical institutions to prevent further distribution of counterfeit products.

The investigation revealed 62 other patients who were dispensed HARVONI Combination Tablets from the franchise pharmacies in Nara but it was confirmed through collaboration by medical institutions that none of the patients took the counterfeit products.

MHLW, in consideration of the fact that such counterfeit products had been sold to a certain cash-only wholesaler by an unidentified person under a false name, issued a notification that mandates wholesalers and pharmacies across the nation to verify the identity of the transferor of drugs and inspect their container and package.

Meanwhile, the supervising local regulatory authorities, in accordance with provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices (PMD Act), ordered all wholesalers and pharmacies involved in the distribution of the counterfeit products to take corrective actions, and among such wholesalers and pharmacies, ordered the pharmacy who had a grave responsibility to have prevented the counterfeit drug distribution incident to suspend operation for a certain period and to replace the administrator of the pharmacy. Likewise, the authorities ordered such wholesalers to suspend operation for a certain period. Furthermore, MHLW ordered the administrator of the pharmacies that purchased, stocked, and sold the counterfeit products to other pharmacies to suspend operation for a certain period in accordance with provision of the Pharmacists Act.

Actions taken for the distribution of counterfeit products of HARVONI Combination Tablets

MHLW, in collaboration with Nara and Tokyo regulatory authorities, took actions (1) to (6).

(1) Investigation of distribution route of the counterfeit products
○ Nara and Tokyo regulatory authorities launched an on-site inspection and seized purchase slips and other evidence. The distribution route of the counterfeit products was virtually identified based on these evidential documents.

(2) Prevention of dissemination by immediate seizure of the counterfeit products and information release
○ Gilead Sciences, Inc. immediately collected 5 counterfeit products found in the franchise pharmacies in Nara. Subsequently, during the investigation of the distribution route in Tokyo, 10 bottles of counterfeit products were seized from the wholesalers.
MHLW concurrently announced to the public and notified medical institutions of the counterfeit products.

(3) Early confirmation of health and safety of patients
○ Confirmation that no patient took the counterfeit drug (Nara regulatory authorities and others[*2] already confirmed by contacting directly all 62 patients who had received HARVONI from all 59 franchise pharmacies since May 2016[*1]).

*1 Time when the pharmacy franchise started purchasing HARVONI from wholesalers who did not have business with Gilead Sciences, Inc.
*2 Wakayama regulatory authorities confirmed that no counterfeit products were dispensed to patient in the medical institution in Wakayama, which returned the counterfeit product distributed from the wholesaler.

(4) Issuance of a notification to prevent recurrence
○ On February 16, MHLW issued a notification through prefectural health authorities that mandates wholesalers and pharmacies to verify the identity of the transferor of drugs and inspect their container and package.

(5) Execution of administrative dispositions
○ All wholesalers and pharmacies involved in the distribution of the counterfeit products were ordered to take corrective actions. Some of the pharmacies were ordered to suspend operation and replace the supervising pharmacist.
Some of the wholesalers were ordered to suspend operation.

(6) Discussion in the committee
○ The "Committee to investigate proper measures against distribution of counterfeit prescription drugs" was established.

3. Discussions in the "Committee to investigate proper measures against distribution of counterfeit prescription drugs"

Responding to the above-mentioned counterfeit drug distribution incident, the "Committee to investigate proper measures against distribution of counterfeit prescription drugs" has discussed since March 2017 to take integrated measures to prevent distribution of counterfeit drugs from manufacturing through distribution. MHLW, based on the discussions in the review committee, revised the related ministerial ordinances in October 2017 for the measures that needed to be taken immediately to prevent counterfeit drug distribution and compiled the discussions so far in the expert review committee in December 2017 into a report.

(1) Details of revision of the ministerial ordinances

MHLW reviewed the system regarding the information that pharmacy proprietors and wholesalers are required to record when transferring or receiving drugs and their obligation to verify the identity of the trading partner.

Three ministerial ordinances were revised as follows:

- ○ Ministerial Ordinance on Partial Revision of Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals and Medical Devices (MHLW Ministerial Ordinance No. 106 of 2017)
- ○ Ministerial Ordinance on Partial Revision of Regulations for Buildings and Facilities for Pharmacies (MHLW Ministerial Ordinance No. 107 of 2017)
- ○ Ministerial Ordinance on Partial Revision of the Ministerial Ordinance to Determine the System for Business of Pharmacies, Shop Sale Business, and Household Distribution (MHLW Ministerial Ordinance No. 108 of 2017)

[Details of revision of the ministerial ordinances]

(1) Revised ordinances additionally specify a method for verifying the identity of the trading partner, lot number, and expiration date, etc. in addition to the product name, quantity, name of the trading partner, and date of trading as the items of information that pharmacy proprietor and wholesalers are required to record when transferring or receiving drugs.

(2) Revised ordinances additionally specify the requirement that each licensed site need to prepare and retain transaction records (e.g. product name, quantity, lot number, expiration date) when drugs are transferred and received between pharmacies founded by the same pharmacy proprietor.

(3) Revised ordinances additionally specify the requirement to identify the name and address of the person (e.g. pharmacy) that has opened the package in the case where a drug is sold or transferred after opening the package sealed by a MAH, except for dispensing.

(4) Revised ordinances additionally specify the requirement that the area where storage facilities are installed need to be clearly separated from other areas as one of the regulations regarding buildings and facilities of pharmacies, shop sale business sites, and sales offices of wholesalers.

(5) Revised ordinances additionally specify the requirement to identify the persons authorized access to the area where drugs storage facilities are installed as one of the regulations regarding the system for selling or transferring drugs in pharmacies, shop sale business sites, and sales offices of wholesalers.

[Date of publication and enforcement]

Date of publication: October 5, 2017

Date of enforcement: January 31, 2018. Of revisions (1) and (2), the revision pertaining to the lot number and expiration date will be enforced on July 31, 2018.

* Please refer to the following URL (MHLW website) for information about revision of the ministerial ordinances and their enforcement notifications (PSEHB Notification No. 1005-1, by the Director-general of Pharmaceutical Safety and Environmental Health Bureau dated October 5, 2017).

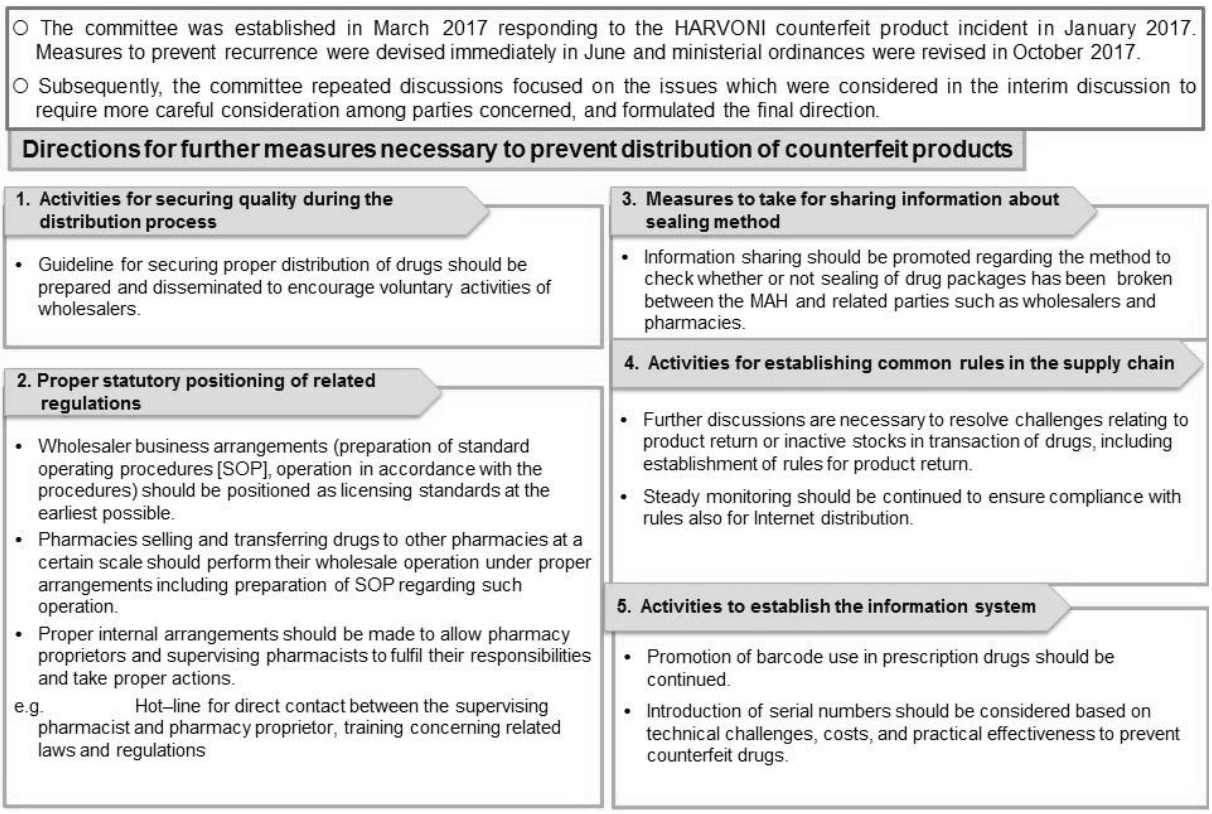
http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000179749.html

(Only available in Japanese language)

(2) Direction for other further measures

Apart from what is mentioned in (1), the review committee formulated the direction for securing quality in the distribution process to prevent recurrence of counterfeit drug distribution.

Final summary of the discussions in the committee to investigate proper measures against distribution of counterfeit prescription drugs



* Please refer to the following URL (MHLW website) for the final report formulated by the review committee to investigate proper measures against distribution of counterfeit prescription drugs.

http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000190026.pdf

(Only available in Japanese language)

4. Government activities to prevent distribution of counterfeit drugs through private import

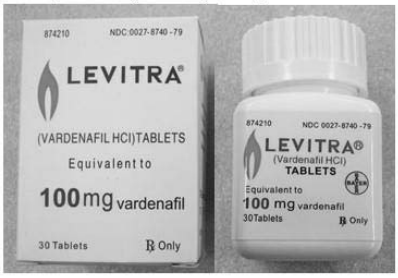
As explained above, the recent incident of the counterfeit HARVONI Combination Tablets is an extremely critical one in which counterfeit drugs penetrate the drug wholesaling route in Japan and were dispensed to patients through pharmacies. Meanwhile, private import over the Internet is considered to be the main route by which counterfeit drugs are supplied to consumers in Japan. This paragraph introduces distribution of counterfeit drugs in Japan mediated by private import and preventive activities.

Counterfeit drugs recently disputed in Japan

○ Products were **ordered by individuals** and **personally imported directly from overseas** sellers via the Internet

- The transaction did not involve any distributors or pharmacist in Japan.
- Internet sellers that received orders had no marketing or other licenses.
- The appearance of the products are apparently different from products distributed in Japan.

<ED (erectile dysfunction) drug>



↑ An ingredient inconsistent with the labeling (sildenafil) was detected.
(Products approved in Japan have PTP package)

↑ An ingredient inconsistent with the approved product (sildenafil) was detected.
(Products approved in Japan have PTP package)

<Slimming drug>

↑ Labeled ingredients were not detected.
(Relevant ingredients are not approved in Japan)

According to the World Health Organization (WHO), more than 1500 reports were received about counterfeit drugs from all over the world including the U.S. and Japan from 2013 to 2017, indicating that the counterfeit drug problem is a serious global public health issue. In EU member nations, 27 cases of counterfeit drug distribution in the regular distribution route and 170 cases in the illegal distribution route were reported from 2002 to 2007, evidencing that the counterfeit drug problem is not an issue unique to developing countries.

These days, it is easy to obtain products marketed overseas from Japan as a result of expansion of Internet commerce, but the risk that counterfeit products are supplied to consumers is considered high for private drug import over the Internet because it is difficult to adequately check in advance that the overseas seller is reliable or not, and because overseas packaging may differ from the package of products marketed in Japan making it difficult to judge the authenticity by the image online.

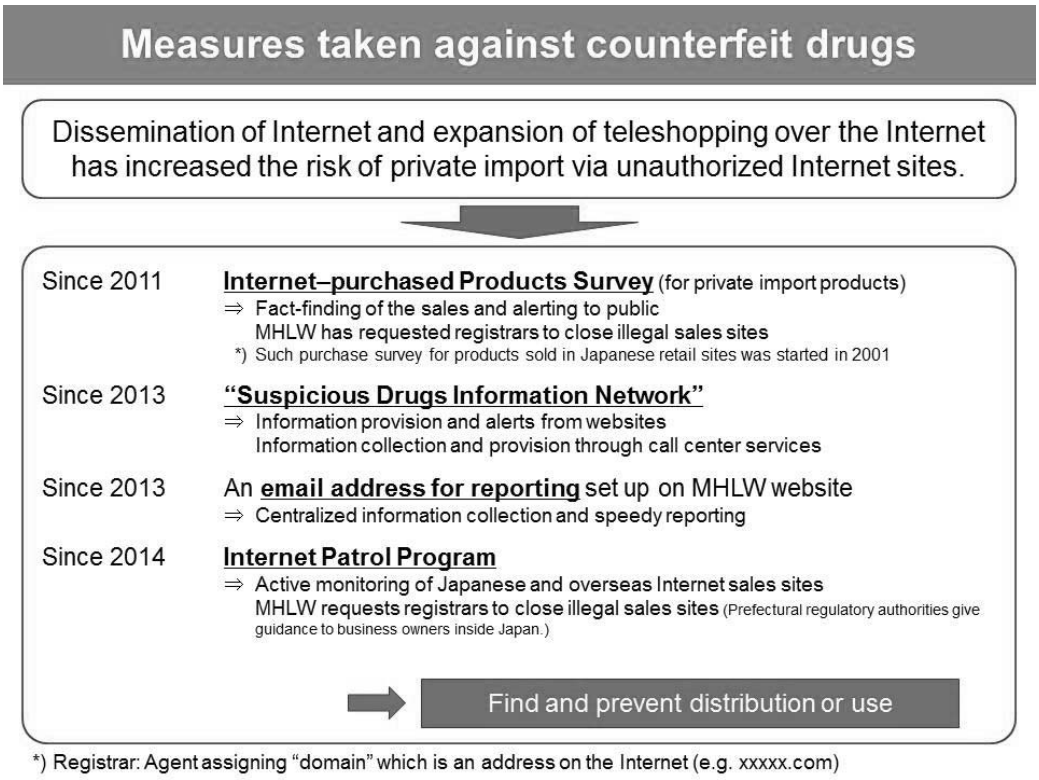
In fact, there are reports of clinically–significant health effects of Japanese consumers caused by overseas counterfeit drugs (Hiroko Izumo, et al.; Journal of the Japan Diabetes Society 54(12) 906-909, 2011).

As measures to address these issues, MHLW has purchased overseas drugs marketed via the Internet, analyzed the authenticity and ingredients, and released the results to increase awareness of Japanese consumers since fiscal year (FY) 2011 (Internet–purchased Products Survey). In FY2014, MHLW purchased via the Internet 10 overseas products for erectile dysfunction (ED) and had the National Institute of Health Sciences (NIHS) analyze the products. Four of the drugs analyzed contained pharmaceutical ingredients inconsistent with the labeling revealing they were counterfeit drugs.

MHLW has outsourced “Suspicious Drugs Information Network” (http://www.yakubutsu.mhlw.go.jp/, only available in Japanese language) since FY2013 to release information about results of such surveys as mentioned above and Japanese translation of such information as released by overseas regulatory authorities on uncovered counterfeit drugs and health effects caused by such counterfeit drugs, etc. to raise caution. The ministry also provides a call center service so that the general public can consult over private drug import and other related issues.

In addition, MHLW has established the system to collect information from the public about marketing of counterfeit drugs and alleged violation of the PMD Act by releasing an email address for reporting on the MHLW website, and since FY2014, has been actively monitoring Japanese and overseas Internet sites selling drugs to citizens living in Japan (Internet Patrol Program) and has been requesting the registrar (agent assigning “domain” which is an address on the Internet) to close the illegal site to prevent inflow of counterfeit drugs into Japan via such illegal sales sites.

MHLW hereby requests consumers to refer to information released on “Suspicious Drugs Information Network” and to refrain from easy private drug import to reduce the risk of being passed off counterfeit drugs and requests healthcare professionals to introduce “Suspicious Drugs Information Network” and provide appropriate advice when consulted by consumers on private import of overseas drugs.



Internet–marketed Products Purchase Survey (FY2014)

[Summary]

○ MHLW purchased products marketed overseas via Internet private import deputizing sites and had the NIHS analyze the products.

*) Apart from those products, "dangerous drugs" and so-called health foods were subject to the survey.

[Results]

○ MHLW purchased 10 products marketed overseas. The analysis revealed that 4 of them contained **pharmaceutical ingredients different from the labeling and that they were counterfeit drugs***

- From a product named "Cialis 50 mg," "41 mg of sildenafil" was detected.
- From a product named "Cialis 20 mg," "20 mg of sildenafil and 10 mg of tadalafil" were detected.
- From a product named "LEVITRA 20 mg," "52 mg of sildenafil and 19 mg of tadalafil" were detected.
- From a product named "LEVITRA 20 mg," "12 mg of tadalafil and 17 mg of avanafil" were detected.

*) Authentic products of Cialis contain tadalafil. Authentic products of LEVITRA contain vardenafil.

Photos of products named "Cialis 50 mg," "Cialis 20 mg," "LEVITRA 20 mg," and "LEVITRA 20 mg" (from left to right)

[Monitoring/control activities]

○ MHLW transmits an alert mail to the site (located overseas) selling a product from which pharmaceutical ingredients inconsistent with the labeling have been detected or selling counterfeit drugs and requests the relevant registrar to delete registration to discontinue sales and advertisement of such products as guidance/regulatory enforcement activities.

Program for proper practice of private import and designated substances (Suspicious Drugs Information Network)

○ Website and hot–line to provide information and increase awareness about private import and designated substances

(Summary of the program)

1. Website to increase awareness

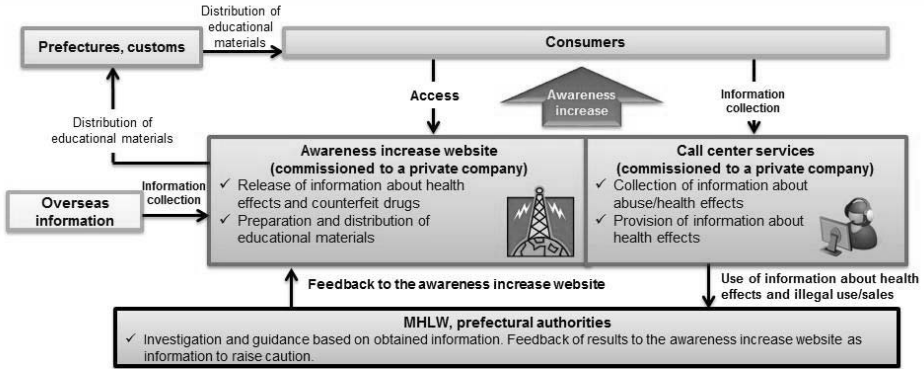
(1) MHLW launched a new appealing website to provide medical doctors and consumers with information about counterfeit drugs and health effects and to raise awareness to in an integrated manner. The website releases in an integrated manner information about counterfeit drugs and health effects collected from related parties in Japan (e.g. MHLW, prefectural authorities, pharmaceutical companies) and overseas regulatory authorities (e.g. U.S. FDA).

(2) MHLW prepares educational materials, releases them on the website, and distributes to prefectural authorities and customs.

2. Call center services (hot–line for private import)

(1) MHLW actively collects information about [1] health effects and [2] abuse/illegal sales to use for educational and vigilance/regulation purposes.

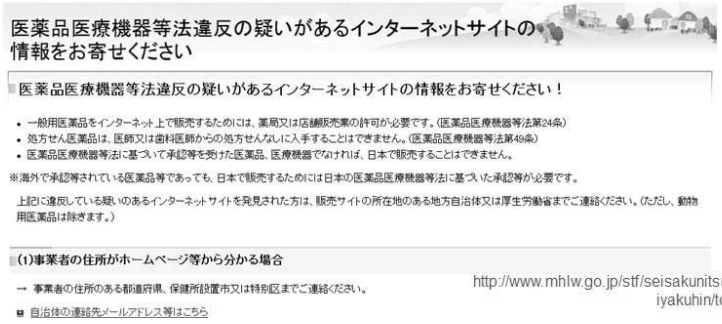
(2) Provision of information about health effects when receiving inquiries



Contact for reporting set up

Progress of activities

- ○ To cope with the anticipated increase of reports regarding illegal Internet drug sales, MHLW set up **an email address for reporting** on its website in January 2013 for centralized information collection and speedy reporting.
- ○ MHLW requested **prefectural authorities,** the entities supposed to respond to incidents as the supervisor of the dealers or other implicated parties if their locations are identified, **to provide their contacts** on the website for speedy reporting.


医薬品医療機器等法違反の疑いがあるインターネットサイトの情報をお寄せください

医薬品医療機器等法違反の疑いがあるインターネットサイトの情報をお寄せください！

- 一般用医薬品をインターネット上で販売するためには、薬局又は店舗販売業の許可が必要です。(医薬品医療機器等法第24条)
- 処方せん医薬品は、医師又は歯科医師からの処方せんなしに入手することはできません。(医薬品医療機器等法第49条)
- 医薬品医療機器等法に基づいて承認等を受けた医薬品、医療機器でなければ、日本で販売することはできません。

※海外で承認等されている医薬品等であっても、日本で販売するためには日本の医薬品医療機器等法に基づいた承認等が必要です。

上記に違反している疑いのあるインターネットサイトを発見された方は、販売サイトの所在地のある地方自治体又は厚生労働省までご連絡ください。(ただし、動物用医薬品は除きます。)

(1)事業者の住所がホームページ等から分かる場合

→ 事業者の住所のある都道府県、保健所設置市又は特別区までご連絡ください。

自治体の連絡先メールアドレス等はこちら

http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp131111-01_1.html

Internet Patrol Program

Summary

- ○ MHLW started a commissioned program for **active monitoring of Japanese and overseas Internet sales sites** (by keyword search) in April 2014.
- ○ If violation of the PMD-Act has been discovered, MHLW **requests** the Internet service provider (e.g. registrar) to **close the violator's site**.

*1) Violation of Article 68 of the PMD Act (Prohibition of Advertisement of pharmaceuticals, etc. before Their Approval) is the legal basis for such a request to close the site.
*2) If the violator is a Japanese business entity, the supervising prefectural authority gives guidance.

Data

- ○ Number of closed sites

	Unapproved drugs	Dangerous drugs	Total
FY2014	105	123	228
FY2015	1 918	24	1 942
FY2016	315	1	316

Alert about unapproved drugs

- Information about counterfeit drugs and other unapproved drugs collected from overseas regulatory authorities and other related parties are released on Suspicious Drugs Information Network to raise caution.

http://www.yakubutsu.mhlw.go.jp/ only available in Japanese language

(source information provided only in Japanese language)

Alert using posters and leaflets

← Poster

↑ Leaflet

(source information provided only in Japanese language)

5 Closing comments

MHLW has been engaged in quality control activities including intercepting counterfeit products in the drug distribution process through activities using “Suspicious Drugs Information Network” and revision of ministerial ordinances in accordance with principles summarized by the “Committee to investigate proper measures against distribution of counterfeit prescription drugs.” MHLW hereby requests healthcare professionals to understand activities to prevent distribution of counterfeit drugs including details of the revision of ministerial ordinances and principles summarized by the expert committee.

Strictly verify identification of the transferor and sealing when transferring and receiving drugs.

In order to prevent the distribution of counterfeit drugs, the Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices have been revised to mandate to verify identification of the transferor when transferring and receiving drug (enforced on January 31, 2018). For the details, please see Enforcement of the Ministerial Ordinance on Partial Revision of Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals and Medical Devices (PSEHB Notification No. 1005-1, by the Director General of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare, dated October 5, 2017)

Verify the drugs, their packaging and containers, and sealing as well and avoid receiving, dispensing, or sale of drugs if any inconsistencies with their usual state are noted.

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated January 11, 2018, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 [1] Teriparatide (genetical recombination)

Brand name (name of company)	[1] Forteo Subcutaneous Injection Kit 600 μg (Eli Lilly Japan K.K.)
Therapeutic category	Thyroid and parathyroid hormone preparations
Indications	[1] Osteoporosis with high risk of bone fracture

PRECAUTIONS (underlined parts are revised)

Important Precautions

Shock, loss of consciousness accompanying acute transient dropped blood pressure, seizures, or fall may occur from immediately after to several hours after administration of this drug. Some cases first occurred after more than several months of treatment. When this drug is administered, patients should be instructed to:

1) Keep as quiet as possible for approximately 30 minutes after administration.
2) Sit or lie down until they recover from the symptoms or signs if decreased blood pressure, dizziness, dizziness on standing up, palpitations, feeling poorly, nausea, facial pallor, or cold sweat occur after administration.

Adverse reactions (clinically significant adverse reactions)

Anaphylaxis: Anaphylaxis (dyspnoea, decreased blood pressure, rash, etc.) may occur. Patients should be carefully monitored. If abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Shock, loss of consciousness: Shock or loss of consciousness accompanying acute transient dropped blood pressure may occur and cases that led to cardiac arrest, respiratory arrest have been reported. If abnormalities are observed, appropriate measures should be taken and discontinuing this drug should be considered from the next dose onward.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 1 year and 7 months (April 2016 to November 2017)

Cases related to cardiac arrest and respiratory arrest [1] 0 case

Cases related to loss of consciousness: [1] 5 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: [1] Approximately 440 000

Launched in Japan: [1] October 2010

[2] Teriparatide acetate (subcutaneous Injection)

Brand name (name of company)	[2] Teribone 56.5 μg for subcutaneous injection (Asahi Kasei Pharma Corporation)
Therapeutic category	Thyroid and parathyroid hormone preparations
Indications	[2] Osteoporosis with high risk of bone fracture

PRECAUTIONS (underlined parts are revised)

Important Precautions

Shock, loss of consciousness accompanying acute transient dropped blood pressure, seizures, or fall may occur, from immediately after to several hours after administration of this drug. Some cases first occurred after more than several months of treatment. Attention should be paid to the following points when this drug is administered.

1) Patient should be monitored for their condition for approximately 30 minutes as closely as possible following administration. Particularly when administering this drug to outpatients, it is desirable to confirm the patients' safety before letting them leave.
2) Patients should be instructed to sit or lie down until they recover from the symptoms or signs if decreased blood pressure, dizziness, dizziness on standing up, palpitations, feeling poorly, nausea, facial pallor, or cold sweat occur after administration.

Adverse reactions (clinically significant adverse reactions)

Anaphylaxis: Anaphylaxis may occur. Patients should be carefully monitored. If abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Shock, loss of consciousness: Shock or loss of consciousness accompanying acute transient dropped blood pressure may occur and cases that led to cardiac arrest or respiratory arrest have been reported. If abnormalities are observed, appropriate measures should be taken and discontinuing administration should be considered from the next dose onward.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 1 year and 7 months (April 2016 to November 2017)

Cases related to cardiac arrest and respiratory arrest
[2] 2 cases (no fatal case)

Cases related to loss of consciousness: [2] 35 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: [2] Approximately 80 000

Launched in Japan: [2] November 2011

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 80s	Osteoporosis (Vertebral compression fracture)	56.5 μg once/week 7 doses ↓ Discontinued	Blood pressure decreased, cardiopulmonary arrest	
				Start of administration	Once weekly administration of teriparatide 56.5 μg was started. At about 30 minutes after administration of teriparatide, blood pressure decreased from 105/– mmHg to 77/46 mmHg. At 1 hour after administration of teriparatide, blood pressure recovered to 100/– mmHg and the patient went home.
				7 days after the start	The patient received the second dose of teriparatide. Blood pressure immediately after administration was 139/– mmHg. Blood pressure at 10 minutes after administration was 100/– mmHg. She got well in 30 minutes after administration and went home.
				14 days after the start	The patient received the third dose of teriparatide. Blood pressure immediately after administration was 103/– mmHg. Blood pressure at 30 minutes after administration was 81/– mmHg. Blood pressure at 1.5 hours after administration was 92/– mmHg. She went home 2 hours after administration.
				21 days after the start	The patient received the fourth dose of teriparatide. Blood pressure immediately after administration was 122/– mmHg. Blood pressure was 118/– mmHg in 30 minutes after administration and she went home.
				26 days after the start	The patient received the fifth dose of teriparatide. Blood pressure immediately after administration was 123/– mmHg. She did not have wobble and went home 30 minutes after administration.
				32 days after the start	The patient received the sixth dose of teriparatide. Blood pressure immediately after administration was 121/– mmHg. Blood pressure at 25 minutes after administration was 100/– mmHg. She went home 1 hour after administration.
				39 days after the start	The patient complained about headache. She did not receive teriparatide.
				47 days after the start (Day of discontinuation)	Blood pressure immediately before administration was 125/– mmHg. The patient had alleviation of headache and received the seventh dose of teriparatide. Blood pressure and pulse rate were 101/51 mmHg and 81 min, respectively. Blood pressure at 30 minutes after administration was 101/– mmHg. At about 70 minutes after administration of teriparatide, she lost strength, fell down, and had cardiopulmonary arrest (at ER), agonal respiration, and cold sweat. Carotid pulses were not palpable at 78 minutes after administration, and cardiopulmonary resuscitation was started. She was successfully resuscitated. At 82 minutes after administration, she regained spontaneous circulation as a result of cardiopulmonary resuscitation, had consciousness level of JCS I–2, blood pressure 149/79 mmHg, pulse rate 95/min, SpO2 (arterial oxygen saturation) 100%, and became able to talk. The patient had no marked change in hematological examinations and echocardiography and no abnormality in electrocardiogram in subsequent follow-ups.
				6 days after discontinuation	She had uneventful progress and was discharged from the hospital. Administration of teriparatide was discontinued.

Laboratory Examination

	Start of administration	Start of administration	Start of administration	7 days after the start	7 days after the start
	-	At 30 minutes after administration	At 1 hour after administration	Immediately after administration	At 10 minutes after administration
Systolic blood pressure (mmHg)	105	77	100	139	100
Diastolic blood pressure (mmHg)	—	46	—	—	—

	14 days after the start	14 days after the start	14 days after the start	21 days after the start	21 days after the start	26 days after the start
	Immediately after administration	At 30 minutes after administration	At 1.5 hours after administration	After administration	At 30 minutes after administration	After administration
Systolic blood pressure (mmHg)	103	81	92	122	118	123
Diastolic blood pressure (mmHg)	—	—	—	—	—	—

	32 days after the start	32 days after the start	47 days after the start	47 days after the start	47 days after the start	47 days after the start
	After administration	At 25 minutes after administration	Before administration -	-	At 30 minutes after administration	At 82 minutes after administration
Systolic blood pressure (mmHg)	121	100	125	101	101	149
Diastolic blood pressure (mmHg)	—	—	—	51	—	79
Pulse rate (/min)	—	—	—	81	—	95
SpO2 (%)	—	—	—	—	—	100

Concomitant medications: loxoprofen sodium hydrate, lansoprazole, indometacin, sitagliptin phosphate hydrate, aspirin, rosuvastatin calcium, glimepiride, sarpogrelate hydrochloride, zopiclone, metformin hydrochloride

2 Edoxaban tosilate hydrate

Brand name (name of company)	Lixiana Tablets 15 mg, 30 mg, 60 mg, Lixiana OD Tablets 15 mg, 30 mg, 60 mg (Daiichi Sankyo Company, Limited)
Therapeutic category	Anticoagulants
Indications	○ Reduction of the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation ○ Treatment and prophylaxis of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) ○ Reduction of the risk of venous thromboembolism in patients undergoing any of the following orthopedic surgeries for the lower limbs: Total knee replacement, total hip replacement, and hip fracture surgery

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Interstitial lung disease:** Interstitial lung disease may occur, sometimes accompanied with bloody sputum or pulmonary alveolar hemorrhage. Patients should be carefully monitored. If any abnormalities such as cough, shortness of breath, dyspnoea, pyrexia, and abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial lung disease is suspected, administration of this drug should be discontinued and appropriate measures such as administration of corticosteroid should be taken.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 6 months (from April 2014 to October 2017) Cases related to interstitial lung disease: 8 cases (1 fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 340 000 Launched in Japan: Lixiana Tablets 15 mg, 30 mg: July 2011 Lixiana Tablets 60 mg: December 2014 Lixiana OD Tablets 15 mg, 30mg, 60 mg: November 2017

Case summary

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Reason for use (underlying diseases/complications /past history)		Clinical course and therapeutic measures
Female 80s	Atrial fibrillation (Sinus node dysfunction, hypertension, hyperlipidemia, cardiac pacemaker placement)	30 mg for 34 days	Interstitial lung disease 5 months before start of administration: No problematic lung permeability finding was observed in both lungs in image diagnosis. No ground–glass opacity was seen. 2 days before start of administration: The patient had atrial fibrillation and was treated with catheter ablation. Day 1 of administration: Twice daily administration of apixaban 2.5 mg 2 tablets was switched to once daily administration of edoxaban tosilate hydrate 30 mg 1 tablet. Day 32 of administration: Hematological examination findings indicated she had anemia (Hb 9.8) but she had no complaint about the symptom. Day 34 of administration (Day of discontinuation): The patient visited the hospital for complaint of feeling of malaise and shortness of breath. X ray showed infiltrative shadow in the lung. Interstitial lung disease and pulmonary alveolar haemorrhage were confirmed. Administration of edoxaban tosilate hydrate was discontinued. 1 day after discontinuation: The patient had no alleviation of symptoms and had deterioration of state of consciousness and was admitted to ICU. She had marked deterioration of lung permeability. Ground–glass opacity was seen in the chest CT. She had traction bronchiectasis. 2 days after discontinuation: At 8:30, the patient underwent tracheal intubation and was kept under artificial respiratory management. She underwent the first dose of steroid pulse therapy (3 days) and received antibiotics. At 11:50, she experienced pneumothorax. Drainage was started. Bronchoscopic found slightly bloody BAL. Administration of ethyl icosapentate was discontinued. She was tested negative in the microbial culture test and other tests for β-D-glucan, influenza antigen, mycoplasma IgM antibody, urinary Legionella antigen, urinary pneumococcus antigen. KL-6: 1108 U/m SP-D: 1510 ng/mL 5 days after discontinuation: The patient had deterioration of renal functions and had hematuria. 8 days after discontinuation: The patient underwent the second dose of steroid pulse therapy (3 days). 12 days after discontinuation: Procalcitonin level was within the normal range (0.15 ng/mL). 13 days after discontinuation: The patient had aggravation of pneumothorax and subcutaneous emphysema. She had gradual deterioration of respiratory conditions. 14 days after discontinuation: FiO2 was set at 100%. 15 days after discontinuation: Blood pressure decreased and noradrenaline administration was started. 16 days after discontinuation: She was confirmed dead at 2:50.
Concomitant medications: flecainide acetate, olmesartan medoxomil, famotidine, sulindac, ethyl icosapentate, flavoxate hydrochloride, amlodipine besilate			

3 Lenvatinib mesilate

Brand name (name of company)	Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Unresectable thyroid cancer

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)	**Acute cholecystitis:** Acute cholecystitis, including acalculous cholecystitis, may occur, and cases that led to gallbladder perforation have been reported. Patients should be monitored carefully, and if abnormalities are observed, appropriate measures should be taken such as drug suspension.
Reference information	The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 2 years and 5 months (from the launch in Japan to October 2017) Cases related to acute cholecystitis: 4 cases (no fatal case) The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 1 000 Launched in Japan: May 2015

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 40s	Follicular thyroid cancer (abnormal thyroid function test)	24 mg for 26 days ↓ Discontinued ↓ 24 mg for 42 days ↓ Suspended ↓ 24 mg for 514 days	Cholecystitis Before start of administration: Presence or absence of Biliary calculus: Not known Biliary sludge: Not known Day 1 of administration: Administration of lenvatinib mesylate 24 mg/day was started. Day 15 of administration: The patient experienced hypertension. Day 25 of administration: The patient experienced nasal bleeding. Day 26 of administration: The patient experienced cholecystitis. She did not undergo surgical treatment. She experienced hepatic impairment. Symptoms: abdominal pain (spontaneous pain, tenderness), epigastric pain, upper abdominal pain Image diagnosis: CT Findings: Gallbladder enlargement Biliary calculus: None (ultrasonography and CT) Biliary sludge: None (ultrasonography and CT) Treatment: sulbactam sodium/ cefoperazone sodium 2 g/day (Day 26 to Day 32) Day 27 of administration: (Day of discontinuation) Administration of lenvatinib mesylate was discontinued. The patient recovered from nasal bleeding. 7 days after discontinuation: The patient recovered from cholecystitis and hepatic impairment. 91 days after discontinuation (Day 1 of readministration) Lenvatinib mesylate 24 mg/day was resumed. 43 after resumed: Administration of lenvatinib mesylate was suspended. 64 days after resumed: Administration of lenvatinib mesylate 24 mg/day was resumed. 78 days after resumed: The patient recovered from hypertension. 578 days after resumed (Day of completion of administration) Administration of lenvatinib mesylate was discontinued.

Laboratory Examination

	Day 1 of administration	Day 15 of administration	Day 26 of administration	Day 27 of administration	7 days after discontinuation	9 days after discontinuation
WBC ($\times 10^3$/ mm^3)	4 160	4 110	5 640	7 300	4 870	4 710
CRP (mg/dL)	0.27	0.88	4.49	8.30	2.68	1.43
AST(IU/L)	33	33	52	33	27	51
ALT (IU/L)	35	31	52	39	46	50
Bilirubin (mg/dL)	0.5	0.8	1.9	1.5	0.4	0.4

Concomitant medications: levothyroxine sodium hydrate

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 80s	Papillary thyroid cancer (hypertension, dementia, diabetes mellitus, abnormal thyroid function test)	24 mg for 14 days ↓ Suspended ↓ 20mg for 4 days ↓ Suspended ↓ 14mg for 55 days	Acute cholecystitis 6 months before administration: Presence or absence of Biliary calculus: None (CT) Biliary sludge: None (CT) Day 1 of administration: Administration of lenvatinib mesylate 24 mg/day was started (introduced under hospitalization). Day 3 of administration: The patient experienced anorexia. She was treated with glucose, electrolytes, amino acid solution, and electrolyte infusion solution. Day 7 of administration: The patient experienced hypertension. CT findings: Mild bladder enlargement was observed but it was not pathologic. Day 14 of administration: No biliary calculus or sludge was observed. CT findings: Bladder enlargement was bigger than on Day 7 but it was not pathologic. Day 15 of administration: Administration of lenvatinib mesylate was suspended. Day 26 of administration: Administration of lenvatinib mesylate was resumed at 20 mg/day. Day 30 of administration: Administration of lenvatinib mesylate was suspended. Day 33 of administration: The patient had alleviation of anorexia. Day 34 of administration: Administration of lenvatinib mesylate was resumed at 14 mg/day. Day 51 of administration: The patient experienced thrombopenia. Day 78 of administration: The patient visited outpatient clinic. She did not complain about abdominal pain. Day 89 of administration (Day of discontinuation): The patient made an emergency visit due to suspected acute cholecystitis. Diagnosis was established based on CT findings. Emergency hospital admission She experienced acute cholecystitis. Administration of lenvatinib mesylate was suspended. Symptoms: She had abdominal pain (tenderness) in the hypochondriac region. She was afebrile. * She had no abnormality 1 week before. Image diagnosis: Ultrasonography and MRI Findings: Marked gallbladder enlargement, gallbladder wall thickening Biliary calculus: None (MRI) Biliary sludge: Present (Ultrasonography) Treatment: Cefmetazole sodium 3 g/day (until 6 days after discontinuation) 4 days after discontinuation: The patient did not recover from hypertension. 14 days after discontinuation: The patient recovered from thrombopenia. 18 days after discontinuation: Despite discontinuation of lenvatinib mesylate and conservative therapy, the patient had no alleviation of acute cholecystitis and underwent laparoscopic cholecystectomy. 37 days after discontinuation: The patient was discharged from the hospital. She recovered from acute cholecystitis.

Laboratory Examination

	10 days before administration	Day 14 of administration	Day 78 of administration	Day 89 of administration	18 days after discontinuation	28 days after discontinuation
WBC ($\times 10^3/mm^3$)	4.8	7.2	4.8	5.5	6.2	3.7
CRP (mg/dL)	0.63	4.00	0.47	0.42	1.32	2.17
AST (IU/L)	15	45	33	33	23	16
ALT (IU/L)	8	40	19	13	10	8
Bilirubin (mg/dL)	0.2	0.7	0.5	0.5	0.5	0.2

Concomitant medications: levothyroxine sodium hydrate

3

Revision of Precautions (No. 291)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs in accordance with the Notifications dated January 11, 2018.

1 Psychotropics

[1] Aripiprazole
[2] Aripiprazole hydrate

Brand name	[1] Abilify Tablets 1 mg, 3 mg, 6 mg, 12 mg, Abilify OD Tablets 3 mg, 6 mg, 12 mg, 24 mg, powder 1%, Abilify oral solution 0.1% (Otsuka Pharmaceutical Co., Ltd.), and the others [2] Abilify prolonged release aqueous suspension for IM injection 300 mg, 400 mg, 300 mg syringe, 400 mg syringe (Otsuka Pharmaceutical Co., Ltd.)
Important Precautions	While it is possible that these events were due to the primary disease, impulse-control disorders such as pathological gambling (continual repeated gambling even though it has socially disadvantageous consequences, such as destruction of personal life), increased sexual urges, compulsive shopping, and binge eating after taking this drug have been reported. Patients and their families should be given a thorough explanation of the symptoms of impulse-control disorder in advance and instructed to consult a physician if symptoms occur. Moreover, patients should be closely monitored for changes in condition or disease state and appropriate measures should be taken if symptoms occur, such as reducing the dosage or discontinuing administration.

2 **Thyroid and parathyroid hormone preparations**

Teriparatide (genetical recombination)

Brand name	Forteo Subcutaneous Injection Kit 600 μg (Eli Lilly Japan K.K.)
Important Precautions	Shock, loss of consciousness accompanying acute transient dropped blood pressure, seizures, or fall may occur from immediately after to several hours after administration of this drug. Some cases first occurred after more than several months of treatment. When this drug is administered, patients should be instructed to: 1) Keep as quiet as possible for approximately 30 minutes after administration. 2) Sit or lie down until they recover from the symptoms or signs if decreased blood pressure, dizziness, dizziness on standing up, palpitations, feeling poorly, nausea, facial pallor, or cold sweat occur after administration.
Adverse reactions (clinically significant adverse reactions)	**Anaphylaxis:** Anaphylaxis (dyspnoea, decreased blood pressure, rash, etc.) may occur. Patients should be carefully monitored. If abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Shock, loss of consciousness:** Shock or loss of consciousness accompanying acute transient dropped blood pressure may occur and cases that led to cardiac arrest, respiratory arrest have been reported. If abnormalities are observed, appropriate measures should be taken and discontinuing this drug should be considered from the next dose onward.

3 **Thyroid and parathyroid hormone preparations**

Teriparatide acetate (subcutaneous injection)

Brand name	Teribone 56.5μg for subcutaneous injection (Asahi Kasei Pharma Corporation)
Important Precautions	Shock, loss of consciousness accompanying acute transient dropped blood pressure, seizures, or fall may occur, from immediately after to several hours after administration of this drug. Some cases first occurred after more than several months of treatment. Attention should be paid to the following points when this drug is administered. 1) Patient should be monitored for their condition for approximately 30 minutes as closely as possible following administration. Particularly when administering this drug to outpatients, it is desirable to confirm the patients' safety before letting them leave. 2) Patients should be instructed to sit or lie down until they recover from the symptoms or signs if decreased blood pressure, dizziness, dizziness on standing up, palpitations, feeling poorly, nausea, facial pallor, or cold sweat occur after administration.
Adverse reactions (clinically significant adverse reactions)	**Anaphylaxis:** Anaphylaxis may occur. Patients should be carefully monitored. If abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Shock, loss of consciousness:** Shock or loss of consciousness accompanying acute transient dropped blood pressure may occur and cases that led to cardiac arrest or respiratory arrest have been reported. If abnormalities are observed, appropriate measures should be taken and discontinuing administration should be considered from the next dose onward.

4 **Anticoagulants**

Edoxaban tosilate hydrate

Brand name	Lixiana Tablets 15 mg, 30 mg, 60 mg, Lixiana OD Tablets 15 mg, 30 mg, 60 mg (Daiichi Sankyo Company, Limited)
Adverse reactions (clinically significant adverse reactions)	**Interstitial lung disease:** Interstitial lung disease may occur, sometimes accompanied with bloody sputum or pulmonary alveolar hemorrhage. Patients should be carefully monitored. If any abnormalities such as cough, shortness of breath, dyspnoea, pyrexia, and abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial lung disease is suspected, administration of this drug should be discontinued and appropriate measures such as administration of corticosteroid should be taken.

5 **Antineoplastics-Miscellaneous**

Ipilimumab (genetical recombination)

Brand name	Yervoy Injection 50 mg (Bristol-Myers Squibb Company)
Adverse reactions (clinically significant adverse reactions)	**Myositis:** Myositis may occur. Patients should be carefully monitored for muscular weakness, myalgia, and increased CK (CPK), and if abnormalities are observed, appropriate measures should be taken such as discontinuing administration of this drug or administering a corticosteroid.

6 **Antineoplastics-Miscellaneous**

Lenvatinib mesilate

Brand name	Lenvima Capsules 4 mg, 10 mg (Eisai Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Acute cholecystitis:** Acute cholecystitis, including acalculous cholecystitis, may occur, and cases that led to gallbladder perforation have been reported. Patients should be monitored carefully, and if abnormalities are observed, appropriate measures should be taken such as drug suspension.

4

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 a new drug. It is imposed that its Marketing Authorization Holder (MAH) is responsible for collecting Adverse Drug Reactions from all of the medical institutions where the drugs are used and 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 ADR. EPPV is specified as a condition of approval.

(As of December 31, 2017)
◎: Products for which EPPV was initiated after December 1, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Eculizumab (genetical recombination)[*1] Soliris for Intravenous Infusion 300 mg	Alexion Pharma G.K.	December 25, 2017
◎	Aminolevulinic acid hydrochloride[*2] Alaglio Divided Granules 1.5 g	SBI Pharmaceuticals Co., Ltd.	December 19, 2017
◎	Palbociclib Ibrance Capsules 25 mg, 125 mg	Pfizer Japan Inc.	December 15, 2017
◎	Belimumab (genetical recombination) Benlysta for I.V. Infusion 120 mg, 400 mg Benlysta for S.C. Injection 200 mg Autoinjector, Benlysta for S.C. Injection 200 mg Syringe	GlaxoSmithKline K.K.	December 13, 2017
◎	Bezlotoxumab (genetical recombination) Zinplava for Intravenous Drip Infusion 625 mg	MSD K.K.	December 8, 2017
◎	Budesonide Rectabul 2 mg Rectal Foam 14 Doses	EA Pharma Co., Ltd.	December 7, 2017
◎	Lonoctocog alfa (genetical recombination) Afstyla I.V. Injection 250, 500, 1000, 1500, 2000, 2500, 3000	CSL Behring K.K.	December 1, 2017
	Glecaprevir hydrate/pibrentasvir Maviret Combination Tablets	AbbVie GK	November 27, 2017
	Rupatadine fumarate Rupafin Tablets 10 mg	Teikoku Seiyaku Co., Ltd.	November 27, 2017
	Avelumab (genetical recombination) Bavencio Intravenous Injection 200 mg	Merck Serono Co., Ltd.	November 22, 2017
	Daratumumab (genetical recombination) Darzalex Intravenous Infusion 100 mg, 400 mg	Janssen Pharmaceutical K.K.	November 22, 2017
	Flutemetamol (^{18}F) Vizamyl Intravenous Injectable	Nihon Medi-Physics Co., Ltd.	November 10, 2017
	Quetiapine fumarate[*3] Bipresso Extended Release Tablets 50 mg, 150 mg	Astellas Pharma Inc.	October 27, 2017
	Sildenafil citrate	Pfizer Japan Inc.	September 27,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Revatio Tablets 20 mg		2017
	Nusinersen sodium[*4] Spinraza Intrathecal Injection 12 mg	Biogen Japan Ltd.	September 22, 2017
	Lyophilized human prothrombin complex concentrate Kcentra for I.V. Injection 500, 1000	CSL Behring K.K.	September 19, 2017
	Teneligliptin hydrobromide hydrate/ Canagliflozin hydrate Canalia Combination Tablets	Mitsubishi Tanabe Pharma Corporation	September 7, 2017
	Amenamevir Amenalief Tab. 200 mg	Maruho Co., Ltd.	September 7, 2017
	Baricitinib Olumiant Tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	September 1, 2017
	Pralatrexate Difolta Injection 20 mg	Mundipharma K.K.	August 30, 2017
	Nusinersen sodium Spinraza Intrathecal injection 12 mg	Biogen Japan Ltd.	August 30, 2017
	Leuprorelin acetate[*5] Leuplin SR for Injection Kit 11.25 mg	Takeda Pharmaceutical Company Limited	August 25, 2017
	Eltrombopag olamine[*6] Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	August 25, 2017
	Lyophilized human antithrombin III concentrate[*7] Kenketu Nonthron 500 for Injection, 1500 for Injection	Nihon Pharmaceutical Co., Ltd.	August 25, 2017
	Florbetapir (^{18}F) Amyvid Injection	Fujifilm RI Pharma Co., Ltd.	August 21, 2017
	Clobetasol propionate Comclo Shampoo 0.05%	Maruho Co., Ltd.	July 11, 2017
	Denosumab (genetical recombination)[*8] Pralia Subcutaneous Injection 60 mg Syringe	Daiichi Sankyo Company, Limited	July 3, 2017
	Fluvoxamine maleate (1) Luvox Tablets 25 mg, 50 mg, 75 mg (2) Depromel Tablets 25 mg, 50 mg, 75 mg	(1) AbbVie GK (2) Meiji Seika Pharma Co., Ltd.	July 3, 2017

*1 Generalized myasthenia gravis (for use only in patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or hemocatharsis)

*2 Visualization of tumor tissues of the non-muscle invasive bladder cancer in transurethral resection of bladder tumor

*3 Depressive symptoms in bipolar disorder

*4 Spinal muscular atrophy

*5 Suppression of progression of congenital bulbospinal muscular atrophy

*6 Aplastic anaemia

*7 Portal vein thrombosis associated with decreased antithrombin III

*8 Suppression of progression of bone erosion associated with rheumatoid arthritis