Pharmaceuticals and Medical Devices Safety Information

No. 374 July 2020

This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (https://www.mhlw.go.jp, only in Japanese).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

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No. 374 July 2020

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

[Outline of Information]

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Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of providers of medical care and pharmaceutical products.

If providers of medical care and pharmaceutical products 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 providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ADR	Adverse drug reaction
ANSI	American National Standards Institute
BIPAP	Biphasic positive airway pressure
CSII	Continuous subcutaneous insulin infusion
ECCJ	Electromagnetic Compatibility Conference Japan
EMC	Electro Magnetic Compatibility
EPPV	Early Post-marketing Phase Vigilance
FDA	The US Food and Drugs Administration
FY	Fiscal year
GAD	General Affairs Division
HPB	Health Policy Bureau
IEC	International Electrotechnical Commission
JCQHC	Japan Council for Quality Health Care
JIS	Japanese Industrial Standards
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MIC	Ministry of Internal Affairs and Communications
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
RF	Radio Frequency
RFID	Radio Frequency Identification
TPN	Total parenteral nutrition

1

Revision of Package Inserts regarding Insulin Vial Preparations

1. Introduction

Insulin is often administered as subcutaneous injection. Insulin pens are typically used for the injection, and co-formulation of total parenteral nutrition (TPN) or peripheral venous infusion solution with insulin and continuous subcutaneous insulin infusion (CSII) therapy are also available as alternatives. Since insulin vial preparations are used for co-formulation with insulin as well as for CSII, medical accidents through the confusion of insulin units are prone to occur. Use of syringes dedicated to insulin vials must be ensured.

Among the cases collected and released by the Project to Collect Medical Adverse Event Information, the Japan Council for Quality Health Care (JCQHC), cases of hypoglycaemia have been reported where use of general purpose syringes instead of syringes dedicated to insulin vials to formulate medication liquid from insulin vial preparations resulted in insulin overdose by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL).

Since reports of such cases have been collected, the package insert of insulin vial preparations has been revised.

This section will outline the past medical safety measures that have called for the use of the syringes dedicated to insulin vials, reporting status of recent incidents caused by the failure to use syringes dedicated to insulin vials, and the current revision of package insert.

2. Previous safety measures

(1) Measures taken by JCQHC

JCQHC, based on the cases reported in the Project to Collect Medical Adverse Event Information, introduced a case where a 100 fold dose was administered by confusing the number of units of insulin per milliliter of liquid (insulin units) with the volume of the liquid (mL) in the JCQHC Medical Safety Information NO.6 (May 2007), and a similar case in the Medical Safety Information No.131 (October 2017) for an alert for misunderstanding of the insulin units.

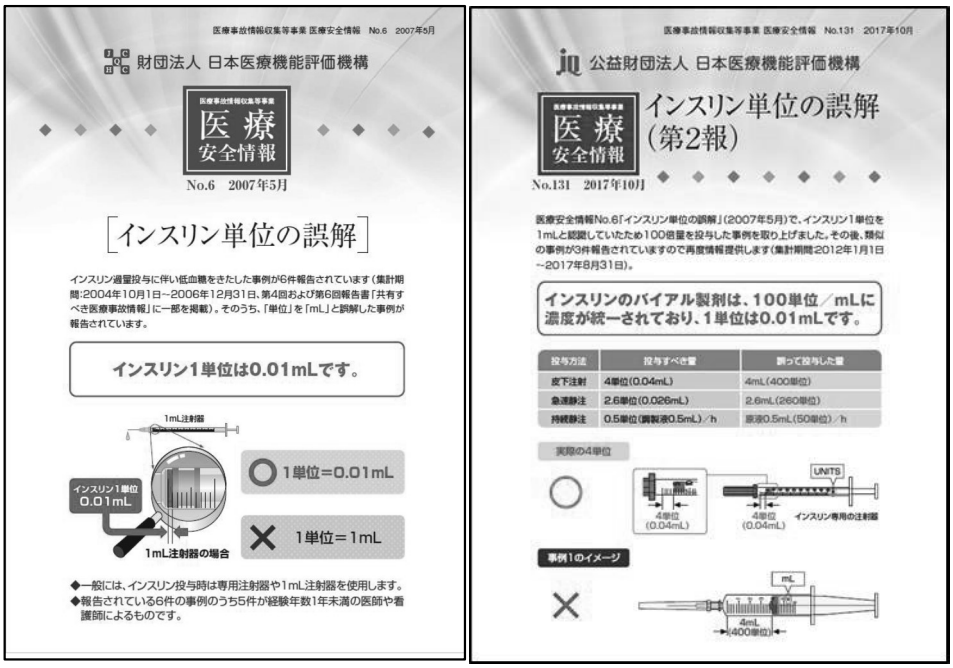

Figure 1 Medical Safety Information No. 6 and No. 131 by the Japan Council for Quality Health Care (only in Japanese)

(2) Measures taken by PMDA

Considering the persistently reported cases of overdose as a result of the use of general purpose syringes, PMDA issued the PMDA Medical Safety Information No. 23 Precaution in Handling of Insulin Syringes (April 2011) to raise awareness of the use of syringes dedicated to insulin vials.

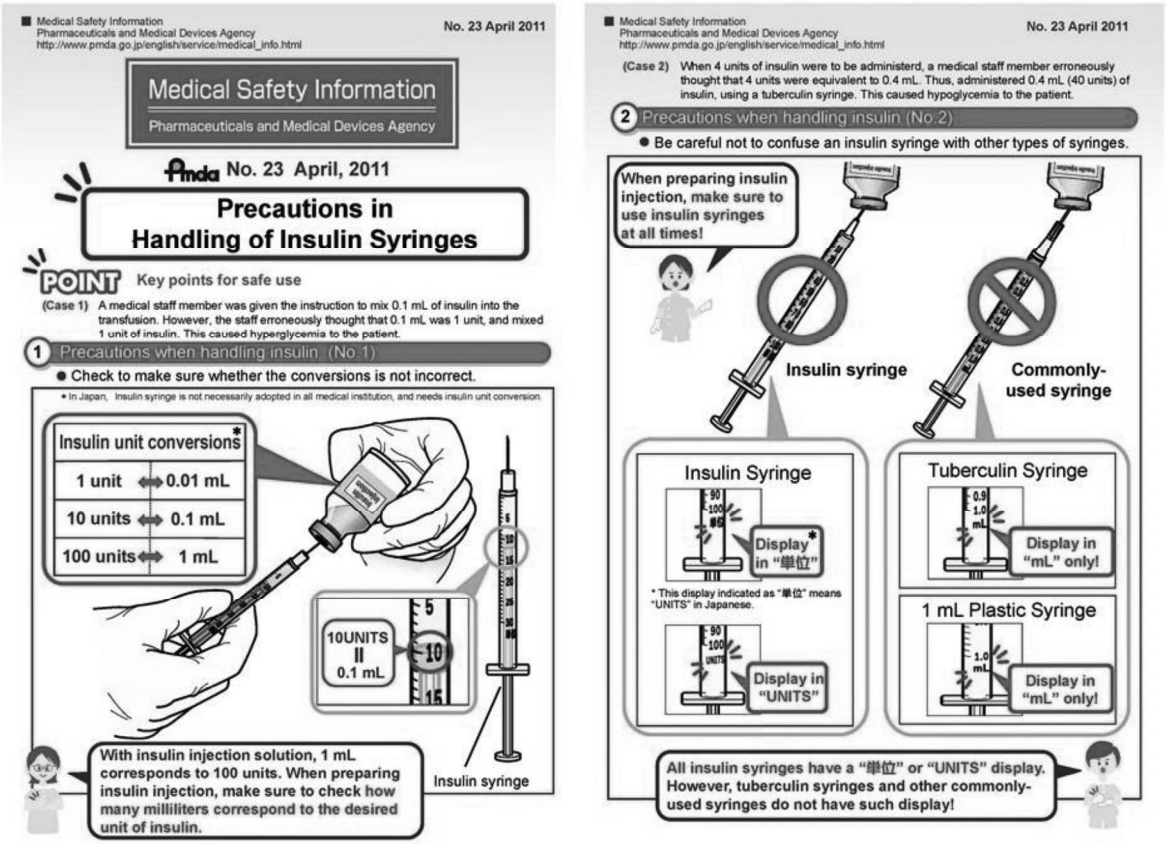

Figure 2 PMDA Medical Safety Information No. 23

(3) Measures taken by MHLW

MHLW issued Manual for Preparation of Standard Operating Procedure for Safe Use of Drugs (HPB/GAD 0330001, PFSB/GAD 0330001, dated March 30, 2007) to make points to be considered in the preparation of Standard Operating Procedure for the safe use of drugs available to the related parties since then.

Recently however, in response to the revisions of laws and regulations concerning medical safety as well as changing environments surrounding the safe use of drugs, the manual was reviewed in the Research concerning the Designing of Standard Operating Procedure for Safe Use of Drugs (the Health and Labour Sciences Special Research Project) and the revised edition of the Manuals for Preparation of Standard Operating Procedure for Safe Use of Drugs (2018) (hereinafter the revised manual) was prepared (Revision of the Manual for Preparation of Standard Operating Procedure for Safe Use of Drugs, Administrative Notice dated December 28, 2018).

The Chapter 7 "Use of Drugs to Inpatients" in the revised manual states for an alert with respect to the delivery of formulated medicines to hospital wards, "drugs that are supplied in vials such as insulin, heparin, or local anesthesia and used in multiple patients or in multiple doses are currently formulated by nurses who respond to the requests without the involvement of pharmacists. It is necessary to define operating procedures from the arrangement for formulation to the administration of such drugs. "For insulin particularly, awareness of proper management and use of dedicated syringes should also be ensured because of the high risk of grave adverse events as a result of confusing insulin units and mL."

3. Reporting status in recent years

The review committee for the safe use of drugs of PMDA discussed the medical accident cases reported between July 1, 2014 and June 30, 2019 as extracted from the descriptive data in the 39th to 58th Reports on the Project to Collect Medical Adverse Event Information, JCQHC, as well as from the data PMDA released on its website. Of the total of 1 654 cases during the previous 5 years, 19 cases were medical accidents involving overdose that resulted from the use of general purpose syringes instead of syringes dedicated to insulin vials to co-formulate insulin. Details of the 19 cases are available in the summary of investigation results prepared by PMDA. (https://www.pmda.go.jp/files/000235075.pdf), accessed on June 15, 2020)

4. The current revision of the package insert

Several alerts have been issued for the persistently reported medical accidents where use of general purpose syringes to formulate insulin from vial preparations led to overdose, as well as the importance of using syringes dedicated to insulin vials. Despite these repeated alerts, cases of overdose resulting from the use of general purpose syringes to formulate insulin are being reported.

Considering these situations, it was decided that "Syringes dedicated to the insulin vials that are calibrated in insulin units should be used to formulate or administer an injection liquid" be added to the Important Precautions section of the package insert of insulin vial preparations for precaution (Revision of Precautions: PSEHB/PSD 0519 No. 1 dated May 19, 2020)

5. Request for cooperation of healthcare professionals

Healthcare professionals are requested to ensure in your medical institutions that dedicated syringes be used to formulate insulin from vial preparations and information be circulated that concentrations of insulin vial preparations are uniformly indicated in 100 units/mL (1 unit = 0.01 mL).

[References]

- Revision of Manual for Preparation of Standard Operating Procedure for Safe Use of Drugs (Administrative Notice dated December 28, 2018) https://www.mhlw.go.jp/topics/bukyoku/isei/i-anzen/hourei/dl/181228-1.pdf (only in Japanese, accessed on June 15, 2020)
- PMDA Medical Safety Information No. 23 Precaution in Handling of Insulin Syringes (April

2011) https://www.pmda.go.jp/files/000153172.pdf (accessed on June 15, 2020)
- JCQHC Medical Safety Information No.6 (May 2007): http://www.med-safe.jp/pdf/med-safe_6.pdf (only in Japanese, accessed on June 15, 2020)
- JCQHC Medical Safety Information No. 131 (October 2017): http://www.med-safe.jp/pdf/med-safe_131.pdf (only in Japanese, accessed on June 15, 2020)
- PMDA website, Revisions of PRECAUSIONS (FY 2020) https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0008.html (accessed on June 15, 2020)
- PMDA website, Notifications related to medical safety measures, Medical safety measures related to drugs and medical devices: https://www.pmda.go.jp/safety/info-services/medical-safety-info/0005.html (only in Japanese, accessed on June 2020)

2
Initiatives to Ensure Safety of Homecare Medical Devices against Radio Waves Emitted by Mobile Phones, etc.

1. Introduction

The effectiveness and safety of medical devices are secured through proper use by healthcare professionals and other relevant parties. There are many electrical devices using radio waves (wireless communication equipment) as wireless network technology has developed in recent years, and they are being used in the daily environment. This situation is also seen in clinical settings. Wireless communication equipment is common in not only medical institutions but also the homecare environment. An increase in the number of wireless communication equipment is expected to continue.

Consequently, it is required to consider in a design and development phase to secure a certain immunity of medical devices to radio waves emitted from mobile phones, etc. in order to ensure the safety of both wireless communication equipment and medical devices and to use them properly at medical institutions. Meanwhile, it is also important that these devices are used under proper management in clinical settings.

Regarding initiatives to promote proper radio wave utilization taken to date, the Electromagnetic Compatibility Conference Japan (ECCJ, a conference that is made up of academic experts, related government agencies, and industry organizations to discuss measures to prevent/eliminate interference of radio frequency with electronic devices and others) established in September 2015, the Radio Wave Utilization Promotion Committee for Medical Institutions (the title was changed in the fiscal year (FY) 2019 to the Committee for the Radio Wave Utilization Promotion for Medical Institutions), and the committee has since continued to discuss the issue. The results of such discussions were published in April 2016 as the Guidance on Safe and Secure Radio Wave Utilization in Medical Institutions (hereinafter referred to as the Guidance). The Guidance was followed by a video and e-learning teaching materials that excerpted its contents released for public awareness and education in April 2018.

On the other hand, there is a concern regarding medical devices used for homecare that wireless communication equipment may be poorly controlled, as opposed to those used in medical institutions. This section introduces trends concerning the initiatives to ensure safety of medical devices used at home against the impact of radio waves from mobile phones, etc. in various countries, and outlines the trend seen in Japan.

2. International trends concerning requirements for electromagnetic immunity of medical devices

Medical devices need to have electromagnetic compatibility (EMC), that is, an adequate level of immunity to render the impact imposed by other wireless communication equipment permissible and also performance that minimizes the electromagnetic waves emitted from inside the medical devices to reduce the impact of such waves on other electrical devices to permissible levels. The notion of EMC is now widely recognized in other countries and the International Standard, IEC60601-1-2, has been established to stipulate the requirements for medical devices.

In Japan, approval of medical devices or acquisition of certifications require conformity to JIS T0601-1-2[2)], the standard introduced in Japan corresponding to IEC60601-1-2, as the criteria for medical-device license/approval[1)] stipulated in the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as the Pharmaceutical and Medical Device Act).

IEC60601-1-2, as mentioned above, is revised on a regular basis, according to changes in the environment where medical devices are used. A revision was made recently, taking into account the necessity of details that assume their use at home in response to the increase of the home use

of medical devices.

The IEC60601-1-2:2014 (the 4th edition), the standard on EMC of medical electrical devices, stipulates the test level in three use environments of “special medical institution environment,” “homecare environment,” and “special environment,” as a standard to stipulate the immunity test level instead of the previous (in the 3rd edition or older) categories of “non-life-supporting equipment” and “life-supporting equipment.” The assumed environment for the “homecare environment” is broadly defined: The house where patients live, outdoor environment, and cars are included. As for the homecare environment, a higher test level is stipulated than that of the special medical environment because the homecare environment is understood as environments with an uncontrolled electromagnetic environment, such as the areas involving unavoidable electromagnetic interference sources compared to special medical institutions, that is, high-risk environments. The marketing authorization holders (MAHs) are required to carry out risk management in which they define the electromagnetic environment where the medical devices are used, identify the risks affecting the safety and functions of medical devices under the defined electromagnetic environment, and determine whether the risk can be accepted through risk evaluation including specific testing.

The 4th edition newly stipulates the immunity test at proximal electromagnetic fields with radio frequency (RF) wireless communication devices to check for any impact when a wireless communication device is placed near a medical device. The new edition highlights the notion of securing safety for the impact of radio waves from wireless communication devices used close to medical devices.

Application of the 4th edition started on January 1, 2019 in Europe and the US. In Japan, JIS T0601-1-2:2018, the Japanese standard corresponding to the 4th edition, was issued on March 1, 2018. There will be a transition period in association with the issuance of JIS T0601-1-2:2018: conformity with the Essential Principles may be confirmed based on the conformity with either the old standard (JIS T0601-1-2:2012) or the new standard (JIS T0601-1-2:2018) until February 28, 2023. Then conformity with the Essential Principles will be determined solely based on the conformity with the new standard effective of March 1, 2023[3)]. It is expected that use of medical devices that conform to the 4th edition will increase and be extensive in Japan and overseas.

3. Trends concerning the electromagnetic wave immunity of medical devices used at home in the US

The U.S. Food and Drug Administration (FDA) started to provide information in the 2000s on medical devices used at home to medical device companies and their users in the US as the provision of medical services at home in the US became more common. The FDA positions medical devices used at home as the ones assumed to be used by users (including patients, care givers, family members, etc.) in any environment other than professional medical institutions, and defines them as Home Use Medical Device, which include devices both for medical institutions and for homecare[4)]. It started the initiatives titled “Home Use Medical Device Initiative” to promote the safety of homecare medical devices (including the notion of EMC in 2010, engaged in various efforts, such as issuance of guidance for MAHs, promotion to provide information on homecare medical devices, and activities to educate the general public).

“Design Considerations for Devices Intended for Home Use-Guidance for Industry and Food and Drug Administration Staff” (issued in 2014 and updated in 2016)[5)] is a guidance that summarizes the points to be considered in design and development for MAHs of Home Use Medical Device. As for EMC, it is recommended to conduct tests in accordance with the ANSI/AAMI/IEC 60601-1-2 Edition 4:2014-02, set the test level based on expected risks under the actual use condition, and identify the devices of possible sources of interference with medical devices (i.e., electric motors, amateur radio transmitters, radio and TV transmitters, radar, anti-theft systems, stereo speakers, mobile phones, RFID, etc.). It is also recommended to present radio wave-specific details of medical devices with wireless communication functions when submitting an application for approval to the FDA and to conduct a test under an environment assumed for such use when other wireless communication equipment will be used in the vicinity of the applying medical devices in order to examine the impact from the wireless equipment using the same frequency band.

The “Electronic Submission of Labeling for Certain Home-Use Medical Devices” (proposed rule) (in 2016)[6)] proposed the MAHs of Class II to III home-use devices to submit electronic data of the

user's manual as well as product labeling information to be stored in the FDA's database, so that the users of home-use devices (patients who receive medical treatment at home, the purchasers of the devices, caregivers, healthcare professionals, etc.) would readily access the precautions on the medical devices.

4. Backgrounds for homecare in Japan

Japan has a long history of homecare promotion. Homecare was started when houses were positioned as a place to provide medical care in the Medical Care ACT revised in 1992. Since then, development of the system to provide homecare services has started, and an item to secure homecare has been added in the statement regarding "Medical Care Plan" which is planned by prefectures, when the Medical Care ACT was revised in 2006. In addition, the Act to Promote Securing Comprehensive Medical and Nursing Care Services, which was established in 2014, stipulates the specialization and collaboration of medical functions at medical institutions for more satisfactory homecare as part of efforts to secure high-quality local medical services and to develop the infrastructure for secured high-quality medical services.

As described above, the system to provide medical services at home has been developed, and medical devices are increasingly used at home. Meanwhile, as wireless communication technologies have been developed, the conventional communication equipment used by wire has become wireless. New wireless products have also been launched, spreading wireless devices quickly at an accelerating pace.

5. Investigation and verification by the Ministry of Internal Affairs and Communications on the impact of radio waves emitted by mobile phones on medical devices

As a consequence of this background, the impact of radio waves emitted from mobile phones, etc. on medical devices used at home is emphasized in Japan, and the Ministry of Internal Affairs and Communications (MIC) is now engaged in an investigation and analysis on the impact.

The MIC has been engaged in an investigation regarding the impact of radio waves on implanted medical devices on a continuous basis since FY 2000.[7)] They also started an investigation on medical devices used for homecare in 2016.

In the investigation for FY 2017, the following 6 types of medical devices were subjected to the assessment of radio wave impact[8)]: General-purpose infusion pump, syringe infusion pump, automatic peritoneal dialyzer, oxygen concentrator, artificial ventilator for adults, and bilevel positive airway pressure units. In the assessment, the operation condition in the typical treatments with them was assumed for sample medical devices and each sensor was set for the maximal possible sensitivity so that results would be produced in the utmost possible favor for the devices' safety profile. Regarding mobile phones, the source of radio waves and the test subjects, they were moved closer to approximately 1 cm from the surface of a medical device after they were set to emit radio waves at the specified output power. The image of the procedures for measurement is provided in Figure 1.

Note that the conditions set for this verification test are much stricter than those of the above-mentioned IEC60601-1-2:2014 (4th edition) and JIS T0601-1-2:2018, the corresponding domestic standard.

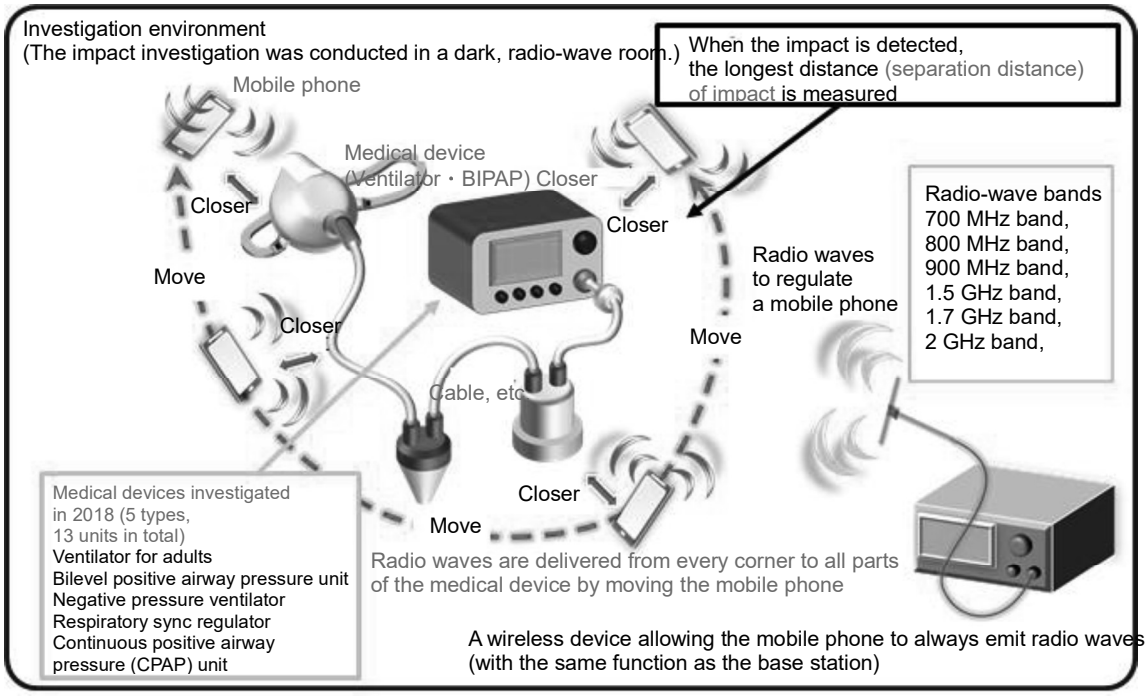

Figure 1 (Source: Ministry of Internal Affairs and Communications)

The investigation results for FY 2017 identified impacts that require close monitoring in ventilators for adults and bilevel positive airway pressure units. In particular, the ventilators for adults erroneously detected spontaneous breathing (an event where the radio waves emitted from a mobile phone, the test subject, were caught by a sensor of the ventilator, which led to misconception of the waves as signals observed along with the patient's breathing). This erroneous detection increased the number of breaths of the patient continuously, the alarm of the ventilator rang, and the number of breaths kept increasing. Of note, this event disappeared after the source of the radio waves was separated from the medical device.

Since the investigation for FY 2017 had a small sample size of ventilators used, an additional verification was carried out in FY 2018, confirming that the risk for occurrence of similar events is independent of the type of device.[9)]

As for this investigation results, a discussion is presented that: Both the ventilator for adults and bilevel positive airway pressure units which were affected by the radio waves emitted by mobile phones detect the patient's respiratory flow, pressure, temperature and humidity, etc. with various sensors. The ventilator circuits in which these sensors are configured need to ensure a certain level of sensitivity of sensors to exert the ventilator's functions, and it may be difficult to take measures such as electromagnetic shielding. It is also discussed that some medical devices may tend to be susceptible to the impact of radio waves due to their mechanistic restrictions.

Although a precaution to prevent the impact of radio waves from mobile phones, etc. is stated in the package insert and the user's manual of the ventilator for adults and bilevel positive airway pressure units which were affected by the radio waves, some of the devices just provide how to calculate the recommended separation distance, with no concrete figures for the distance themselves.

The reports on the Investigations regarding the Impact of Radio Waves on Implanted Medical Devices and Homecare Medical Devices, etc. up to FY2018 (hereinafter "the Reports") provide verification results that identified reversible malfunctions that occurred due to radio waves when a mobile phone was brought very close to ventilators for adults and bilevel positive airway pressure units under the most strict conditions, such as the strongest radio wave emission sent by the mobile phone and the maximal sensor sensitivity set in the medical devices, the specimen. In addition, the Reports state it is important for the MAHs, etc. of medical devices to provide healthcare professionals with sufficient information including details of the recommended separation distance and to ensure the dissemination of such information from healthcare professionals to the patients, their families, caregivers, etc. in order to avoid the impact of radio waves on medical devices.

6. Efforts for safer use of medical devices at home

6.1 Revision of Precautions for ventilators, etc. expected to be used at home

Based on these analysis results in Japan, as for ventilators, etc. (including ventilators for adults and bilevel positive airway pressure units) expected to be used at home, a cautionary statement regarding the ventilators, etc. expected to be used at home is to be added in the section of Important Precautions of Precautions[1011)] in the package insert so that the MAHs will provide information to medical institutions, etc. properly and more smoothly.

To be more specific, since the radio waves may interfere with the operation and a malfunction may result when a mobile phone, etc. (including smartphones, tablet-type devices) is brought closer to these devices than a certain distance, the behavior of the device should be carefully monitored. In addition, the users and their families or other caregivers should be instructed to routinely monitor the device. “A certain distance” is the separating distance for individual ventilators, etc. calculated by their MAHs. The MAHs should confirm the compliance status of the individual ventilators, etc. either with the standard specified by IEC 60601-1-2 or JIS T0601-1-2 as the basis for the calculation. In association with the revision of the package inserts as mentioned above, it is required to carefully explain the conditions for the verification test of the Reports when the MAHs explain to medical institutions, etc. about supplementary contents that cover provided information. It is also required to explain the necessity of routinely monitoring the operation of the device as well as the risks associated with radio wave interference, taking properly into account the contents of the Reports that the medical device was synchronized with the radio wave of a mobile phone and thereby an erroneous detection of spontaneous breathing occurred when the phone was brought very close to the medical device under the most strict test conditions, such as the strongest radio wave emission sent by the mobile phone, the test subject, and the maximal sensitivity set in the medical devices.

6.2 Information leaflets to the users, their families or other caregivers

Information provision by the MAHs of medical devices to healthcare professionals in medical institutions, etc. is important in terms of securing their proper use and providing appropriate medical care to patients safely. It should be applied to homecare, too. It is important to fully understand how to use medical devices properly and what points healthcare professionals, patients, their family, etc. should pay attention to before the devices are used at home.

Therefore, the PMDA Alert for Proper Use of Medical Devices (hereinafter, “the leaflet”) was compiled in July 2020 as a material for proper instructions on the points to which healthcare professionals, patients, their families, etc. should pay attention at home when using a mobile phone, etc. close to an artificial ventilator and/or bilevel positive airway pressure unit expected to be used at home.

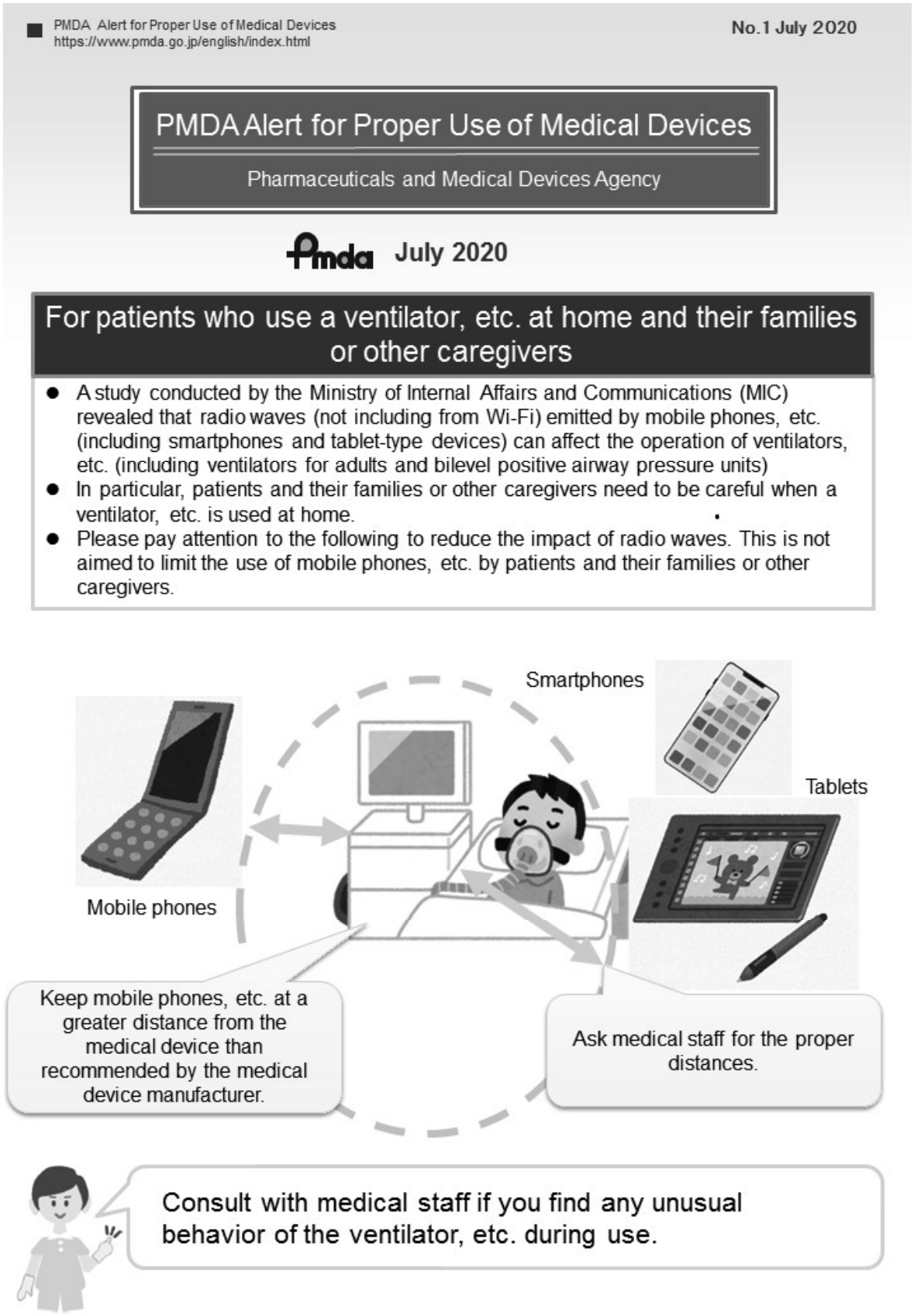

Figure 2-1 Leaflet (The front)

■ PMDA Alert for Proper Use of Medical Devices
https://www.pmda.go.jp/english/index.html

No.1 July 2020

Points to be considered by medical staff

Please read the following before giving an explanation to your patients

- ☐ The top page of this leaflet is intended to show patients when medical staff give an explanation to patients, including their families or other caregivers, who start treatment with a ventilator, etc. (including ventilators for adults or bilevel positive airway pressure units) at home.
- ☐ Verification by the MIC regarding the impact of radio waves emitted by mobile phones on medical devices
  - The MIC is conducting a verification test to examine the impact of radio waves emitted by mobile phones (smartphones, tablets, etc.) on the behavior of medical devices.
  - A test result demonstrated events in which ventilators for adults and bilevel positive airway pressure units erroneously detected radio waves emitted by a mobile phone as the patient's spontaneous breathing when the phone was brought very close to the medical device. (Fiscal year 2017, 2018)

URL:https://www.tele.soumu.go.jp/j/sys/ele/seitai/chis/index.htm (only in Japanese)

This test **assumes extreme situations, which will not be necessarily reproduced in the clinical settings**. We are not aware of any identical events that actually occurred in the clinical settings. **The convenience of the mobile phone for patients and their families or other caregivers will not be limited** based on this test.

- ☐ **The package insert of the applicable medical devices provides the following** regarding the distance to be kept between a mobile phone and a ventilator, etc.

> [Important Precautions]
> ▲. When a mobile phone, etc. (including smartphones, tablets, etc.) is brought close to this device within approximately XX meters, the radio waves may interfere with the operation of the device and a malfunction may result. The behavior of the device should be carefully monitored. Patients and their families or other caregivers should be instructed to conduct a routine check of the device's behavior. [This product has been proven to comply with ****.]
>
> **** is the name of the relevant standard specified by JIS (Japanese Industrial Standards) or IEC (International Electrotechnical Commission).

The distance stated in the package insert was calculated by the manufacturer of the medical device based on the JIS standard, etc. **The medical staff are requested to give the following instructions to the patients and their families or other caregivers.**

- ✓ Use a mobile phone, etc. from the distance instructed by the manufacturer of the ventilator, etc.
- ✓ Check the routine behavior of the ventilator.

- ☐ If there is any malfunction observed in the operation of the ventilator, etc. possibly attributed to radio waves emitted by a mobile phone, etc., please contact the staff of the manufacturer of the medical device.

Published by the Pharmaceuticals and Medical Devices Agency

Contact: Division of Safety for Medical Devices, Office of Manufacturing Quality and Vigilance for Medical Devices
TEL 03-3506-9030 (Direct contact)
FAX 03-3506-9405
https://www.pmda.go.jp/english/index.html

Figure 2-2 Leaflet (The reverse)

This leaflet (Figure 2) provides a summary of instruction details for patients and their families or other caregivers on the front page and points to be considered for healthcare professionals in charge of guidance for patients and their families or other caregivers on the reverse page. Both the front and reverse pages provide the following information with a special consideration given in terms of risk communication so that healthcare professionals, patients, and their families or other caregivers can readily understand the contents:

The front page entitled “For patients who use a ventilator, etc. at home and their families or other caregivers” communicates the risk of impact on the operation of ventilators, etc. that MIC’s verification confirmed and that patients and their families or other caregivers need to be careful of regarding the use of mobile phones while using a ventilator, etc. at home.

The leaflet also notes that the precaution does not limit the use of a mobile phone, etc. by patients and their families or other caregivers. These statements are carefully written so that the facts will be succinctly notified with no overstatement or understatement and patients and their family will not feel too worried about the impact of radio waves.

Based on the information given, as the primary educational contents on the front page, users are advised to use the phone at a greater distance than recommended by the manufacturer of the medical device in the package insert when using a mobile phone around the ventilator or bilevel positive airway pressure unit. The leaflet also suggests that medical professionals provide specific separating distances.

The reverse page is compiled for healthcare professionals to quickly understand necessary information sufficient for giving an explanation to their patients and their families or other caregivers during busy working hours. The first part says, as the intended use of this leaflet, that the front page is positioned to show patients when medical staff give an explanation to patients, including their families or other caregivers, who start treatment with a ventilator, etc. at home.

In the next part, the MIC’s verification details are provided regarding the impact of radio waves emitted from a mobile phone on medical devices, explaining an MIC’s verification test result of events that ventilators for adults and bilevel positive airway pressure units erroneously detected radio waves emitted by a mobile phone, the test subject, as a patient’s spontaneous breathing when the mobile phone, the test subject, was brought very close to the device. This statement also carefully and clearly mentions, as an important supplementary comment in the form of speech bubbles with pictures of a healthcare professional that this verification test assumes extreme situations, which will not be necessarily reproduced in clinical settings, no identical events that actually occurred in clinical settings have been reported, and the convenience of the mobile phone, etc. for patients and their families or other caregivers will not be limited based on this test.

Following this, the leaflet specifically quotes the precaution in the package insert of the applicable ventilators, etc. regarding the distance between a mobile phone, etc. and these medical devices, with some examples. This arrangement is for healthcare professionals to be able to quickly find the necessary part in the package insert of the relevant ventilators, etc. The statement also has an important supplementary comment that the distance provided in the package insert was calculated based on the JIS standards, etc. by the MAH, and highlights the following two points for routine instructions from healthcare professionals to patients. 1) Use a mobile phone, etc. from the distance instructed by the manufacturer of the ventilator, etc., and 2) check the routine behavior of the ventilator, etc.

7. Conclusion

Homecare is expected to increase its share continuously, and also technical innovation is expected to increase the opportunity to use wireless communication equipment around medical devices. While we adapt ourselves to such a changing environment, safer and more effective medical devices are being developed constantly. At the same time, evaluation is underway on the impact of radio waves emitted from wireless communication equipment on medical devices.

The safety regarding the impact of external radio waves on medical devices should be primarily addressed by the MAHs of the devices. At the same time, it is important for users to use the devices properly, taking into account their limited performance in the immunity to electromagnetic waves for example. Cooperation of healthcare professionals and other relevant parties is required as well for the establishment of a system to further ensure proper use of medical devices.

[References]

1) Criteria for Medical Devices stipulated by the Minister of Health, Labour and Welfare in accordance with the provisions in Article 41, section 3 of the Pharmaceutical and Medical Device Act (Ministerial Announcement No. 122 2005)
2) Handling in the Pharmaceuticals Affairs Law in line with the Revision of the Japanese Industrial Standards concerning the Electromagnetic Immunity of Medical Devices (Notification 0328 No. 1 by the Director of Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceuticals and Food Safety Bureau, MHLW, dated March 28, 2012)
3) Handling of the Revision of the Japanese Industrial Standards concerning the Electromagnetic Immunity of Medical Devices (Notification by the Director of Medical Devices Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated March 1, 2018)
4) FDA, "Home Use Devices" https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/HomeUseDevices/default.htm (confirmed on June 22, 2010)
5) FDA, "Design Considerations for Devices Intended for Home Use – Guidance for Industry and Food and Drug Administration Staff," November 2014" https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-devices-intended-home-use
6) FDA, "Electronic Submission of Labeling for Certain Home-Use Medical Devices," October 2016 https://www.federalregister.gov/documents/2016/10/17/2016-25026/electronic-submission-of-labeling-for-certain-home-use-medical-devices
7) Confirming the Conformity of Current Mobile Phones with the Radio Wave Protection Standards-Investigation Results of the Conformity of Mobile Phones with the Radio Wave Protection Guidelines, released by the Telecommunications Bureau, Ministry of Internal Affairs and Communications, dated May 15, 2001 https://www.tele.soumu.go.jp/resource/j/ele/medical/12.htm (only in Japanese, confirmed on June 16, 2020)
8) Report on the Investigation of the Impact of Radio Waves on Implantable Medical Devices and Medical Devices for Home Use etc., Ministry of Internal Affairs and Communications, March 2018 https://www.tele.soumu.go.jp/resource/j/ele/medical/h29.pdf (only in Japanese, confirmed on June 16, 2020)
9) Report on the Investigation of the Impact of Radio Waves on Implantable Medical Devices and Medical Devices for Home Use etc., Ministry of Internal Affairs and Communications, March 2019 https://www.tele.soumu.go.jp/resource/j/ele/medical/h30.pdf (only in Japanese, confirmed on June 16, 2020)
10) Revision of Precautions for Artificial Ventilator, etc. Expected to be Used at Home (PSEHB/MDED No.1122-1 and PSEHB/PSD No.1122-2 Joint Notification by the Director of Medical Device Evaluation Division, and Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated June 16, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Memantine hydrochloride

Branded name (name of company)	Memary Tablets 5 mg, 10 mg, 20 mg, Memary OD Tablets 5 mg, 10 mg, 20 mg, Memary Dry Syrup 2% (Daiichi Sankyo Co., Ltd.) , and the others
Therapeutic category	Central nervous system agents-miscellaneous
Indications	Control of the progression of moderate to severe dementia of the Alzheimer's type

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse Reactions Clinically Significant Adverse Reactions (newly added)

Bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia:
Bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measure should be taken such as discontinuing administration of this drug.

[Under new instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 46-month period (April 2016 to January 2020)
Cases involving bradyarrhythmia: 2 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 400 000
Japanese market launch: June 2011

Case 1

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
1	Male 70s	Higher brain dysfunction (dementia Alzheimer's type, gastrooesophageal reflux disease, cerebration impaired, symptomatic epilepsy, influenza encephalopathy, hypertension, type 2 diabetes mellitus)	5 mg for 8 days ↓ 10 mg for 7days ↓ 20 mg for 45 days	Complete atrioventricular block	
				Day of start of administration	Administration of memantine hydrochloride 5 mg was initiated for higher brain dysfunction. The patient had no history of heart disease.
				Day 9 of administration	The dose was increased to 10 mg.
				Day 16 of administration	The dose was increased to 20 mg
				Day 30 of administration	Pulse rate was: 82 beats/min
				Day 33 of administration (day of onset)	Bradycardia appeared (continued thereafter). Pulse rate: 50 beats/min
				Day 35 of administration	Pulse rate: 44 beats/min
				Day 37 of administration	Pulse rate: 41 beats/min
				Day 43 of administration	Pulse rate: 39 beats/min
				Day 52 of administration	The electrocardiogram showed complete atrioventricular block. A cardiologist diagnosed the patient with an indication for a pacemaker. The day of surgery was decided.
				Day 53 of administration	Side effects were suspected and mianserin hydrochloride tablets was discontinued, but the patient's conditions did not improve. Pulse rate: 43 beats/min
				Day 54 of administration	Chlorpromazine hydrochloride tablets was reduced, but the patient's conditions did not improve.
				Day 60 of administration (day of dis-continuation)	Memantine hydrochloride was discontinued. Pulse rate: 36 beats/min
				1 days after discontinuation	Bradycardia improved. The outcome was recovery.
				2 days after discontinuation	Pulse rate: 70 beats/min
				5 days after discontinuation	The patient revisited the department of cardiology. The patient was told that he returned to a sinus rhythm and bradycardia could be drug-induced. The patient's pacemaker was discontinued.
				21 days after discontinuation	The patient had no symptom development.
	Concomitant drugs: Fursultiamine, levetiracetam, magnesium oxide, lansoprazole, sitagliptin phosphate hydrate, allopurinol, mosapride citrate hydrate, amlodipine besilate, mianserin hydrochloride, chlorpromazine hydrochloride				

Case 2

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
2	Male 70s	Frontotemporal dementia (renal failure chronic, hypertension, diabetes mellitus, renal impairment, abdominal aortic aneurysm, aorta substitution, pollinosis)	5 mg for 8 days ↓ 10 mg for 7 days ↓ 15 mg for 7days	Bradycardia	
				45 days before administration	The patient was admitted to the reporting institution for frontotemporal dementia (the patient has renal failure chronic before admission)
				Day 1 of administration	Memantine hydrochloride (5 mg, once daily) was initiated for frontotemporal dementia.
				Day 9 of administration	The dose was increased to 10 mg.
				Day 16 of administration	The dose was increased to 15 mg.
				Day 21 of administration	The patient started wobbling at night.
				Day 22 of administration (day of discontinuation)	His wobbling was very severe, and the patient was unable to walk. The patient's consciousness was clear, and he could communicate smoothly. But vital sign measurement in the morning showed decreased blood pressure and bradycardia (systolic blood pressure in the 70 range, 40 bpm). The electrocardiogram showed a junctional rhythm whose pulse rate level was 40. Dopamine hydrochloride was initiated. All the oral medicines were discontinued.
				1 day after discontinuation	Hypotension and bradycardia resolved.
				12 days after discontinuation	Dopamine hydrochloride was discontinued, but no problems were noted in blood pressure and pulse.
	Suspected concomitant drugs: Magnesium oxide Concomitant drugs: Amlodipine besilate, alfacalcidol, vonoprazan fumarate, an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus, febuxostat, mecobalamin, mirtazapine, rosuvastatin calcium, calcium polystyrene sulfonate, aspirin, teneligliptin hydrobromide hydrate, yokukansan, suvorexant, linagliptin, aspirin/dialuminate				

2 Bevacizumab (genetical recombination) including the biosimilars

Branded name (name of company)	Avastin for Intravenous Infusion 100 mg/4 mL, 400 mg/16 mL (Chugai Pharmaceutical Co., Ltd), and the biosimilars
Therapeutic category	Antineoplastics-miscellaneous
Indications	Incurable, unresectable, advanced/recurrent colorectal cancer, unresectable, advanced/recurrent non-small cell lung cancer except for squamous cell carcinoma, ovarian cancer, advanced or recurrent cervical cancer, inoperable or recurrent breast cancer; malignant glioma

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse Reactions Clinically Significant Adverse Reactions (newly added)

Artery dissection: Artery dissection including aortic dissection may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

[Under new instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Artery dissection: Artery dissection including aortic dissection may occur.

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 47-month period (April 2016 to March 2020)
Cases involving artery dissection: 1 (No patient mortalities)
The number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 75 000.
Japanese market launch: June 2007

Case

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		No.	
1	Female 60s	Rectal cancer		Acute aortic dissection [Patient background] Metastasis sites: Lung (right lower lobe), bone (sacrum) Pretreatment drug: Folinate-tegafur-uracil therapy, combination of tegafur-gimeracil-oteracil potassium + oxaliplatin therapy Surgical history: Abdominoperineal resection + colostomy (Miles surgery), thoracoscopy-assisted left upper lobectomy, resection of mesenteric tumors, right lower lobe partial resection Radiotherapy: Dose: 60 Gy (in the pelvis) Smoking history: Yes (from 20s to 30s/10 years) Hypertension/hyperlipidaemia/infection: None	
				Day 1 of administration	Bevacizumab was used as the 3rd line therapy.
				28 days after administration	Thrombocytopenia/leukopenia (Grade: 3) caused by bevacizumab appeared.
				182 days after Administration (day of discontinuation)	Bevacizumab was discontinued.
				35 days after discontinuation	Thrombocytopenia/leukopenia was resolving.

				1379 days after discontinuation (day 1 of re-administration)	Bevacizumab was resumed.
				546 days after re-administration (21 days after termination of re-adminstration)	Bilateral multiple increased lung metastasis, 4-cm hepatic cysts in the hepatic lateral segment, bilateral renal cysts were found by CT scan.
				23 days after termination of re-administration	Acute aortic dissection (Grade:5) developed The patient's moaning was noticed and she was found lying on the ground. The patient was transported by ambulance. Consciousness disturbed Ⅰ-1, left paresis, dyslalia, right conjugate deviation were noted. Since stroke was suspected, CT scan and MRI were performed. Acute cerebral infarction due to right internal carotid artery closure was noted. An abdominal ultrasound revealed a flap in the aortic aneurysm. Abdominal CT scan revealed acute aortic aneurysm dissection and the patient was diagnosed with cerebral infarction accompanied by it. In addition to the patient's deteriorating physical condition, cerebral infarction was extensive. Therefore, it was judged that the patient was not indicated for surgery. The patient was admitted to the hospital for observation. [Diagnosis of acute aortic dissection] X-ray inspection revealed cardiomegaly was present and nodular shadows were scattered on lung. CT scan showed dissection reaching ascending aorta to left common iliac artery, brachiocephalic artery and left subclavian artery. No right common carotid artery is delineated. Left kidney had poor contrast except for a part of the upper pole. The effect of dissection reached left renal artery. An abdominal ultrasound revealed a flap in the aortic aneurysm.
			7.5 mg/kg× once every 4 weeks/64 days ↓ discontinued. ↓ 5 mg/kg× once every 4 weeks/29 days ↓ discontinued ↓ 5 mg/kg× once every 4 weeks/526 days	24 days after termination of re-adminstration. (death)	Consciousness level Ⅱ-10 The patient could utter words when she was spoken to, but they were not clear. A small amount of saliva like vomit was noted. The patient's complexion was bad. Laboured respiration was noted. The patient died.

Laboratory test values:

	Day 1 of re-administration	548 days after re-administration (23 days after termination of re-administration)	24 days after termination of re-administration	24 days after termination of re-administration	24 days after termination of re-administration
Blood pressure (systolic) (mmHg)	114	129	192	185	51
Blood pressure (diastolic) (mmHg)	82	56	90	95	30
Fibrin d dimer (μg/mL)	-	20.5	-	-	-

Concomitant drugs: Tegafur/gimeracil/oteracil potassium, irinotecan hydrochloride hydrate, trifluridine/tipiracil hydrochloride

4
Revision of Precautions (No.314)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated June 16, 2020.

1 Central nervous system agents-miscellaneous
Memantine hydrochloride

Branded name	Memary Tablets 5 mg, 10 mg, 20 mg, Memary OD Tablets 5 mg, 10 mg, 20 mg, Memary Dry Syrup 2% (Daiichi Sankyo Co., Ltd.), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia**: Bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measure should be taken such as discontinuing administration of this drug.
[Under New instructions]	
11. ADVERSE REACTIONS 11.1. Clinically Significant Adverse Reactions (newly added)	Bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia

2 Antineoplastics-miscellaneous
Bevacizumab (genetical recombination)
Bevacizumab (genetical recombination) [Bevacizumab biosimilar 1]
Bevacizumab (genetical recombination) [Bevacizumab biosimilar 2]

Branded name	Avastin for Intravenous Infusion 100 mg/4 mL, 400 mg/16 mL (Chugai Pharmaceutical Co., Ltd), and the biosimilars
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Artery dissection**: Artery dissection including aortic dissection may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS 11.1. Clinically Significant Adverse Reactions (newly added)	**Artery dissection**: Artery dissection including aortic dissection may occur.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 30 June, 2020)
◎: Products for which EPPV was initiated after June 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Fluticasone propionate/formoterol fumarate hydrate Flutiform 50 Aerosol 56 puffs, 120 puffs	Kyorin Pharmaceutical Co.,Ltd.	June 29, 2020
◎	Semaglutide (genetical recombination) Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD	Novo Nordisk Pharma Ltd.	June 29, 2020
◎	Tolvaptan*1 Samsca tablets 7.5 mg, 15 mg, 30 mg, Samsca OD tablets 7.5 mg, 15 mg, 30 mg, Samsca granules 1%	Otsuka Pharmaceutical Co., Ltd.	June 29, 2020
◎	Landiolol hydrochloride*2 Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	June 29, 2020
◎	Levothyroxine sodium hydrate Thyradin-S I.V. Injection 200 μg	Aska Pharmaceutical. Co., Ltd.	June 29, 2020
◎	Delgocitinib Corectim Ointment 0.5%	Japan Tabacco Inc.	June 24, 2020
◎	Melatonin Melatobel granules 0.2% for pediatric	Nobelpharma Co., Ltd.	June 23, 2020
◎	Insulin lispro (genetical recombination) Lyumjev Injection Cart, Lyumjev Injection MirioPen, Lyumjev Injection MirioPen HD Lyumjev Injection 100 U/mL	Eli Lilly Japan K.K.	June 17, 2020
◎	Insulin glargine (genetical recombination)/lixisenatide Soliqua Injection SoloStar	Sanofi K.K.	June 8, 2020
◎	Tepotinib hydrochloride hydrate Tepmetko Tablets 250 mg	Merck Biopharma Co., Ltd	June 1, 2020
	Nintedanib ethanesulfonate*3 Ofev capsules 100 mg, 150 mg	Boehringer Ingelheim Japan, Inc.	May 29, 2020
	Darolutamide Nubeqa tablets 300 mg	Bayer Yakuhin Ltd	May 26, 2020

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Trastuzumab deruxtecan (genetical recombination) Enhertu for intravenous drip infusion 100 mg	Daiichi Sankyo Co., Ltd.	May 25, 2020
Brolucizumab (genetical recombination) Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	May 25, 2020
Dotinurad Urece Tablets 0.5 mg, 1 mg, 2 mg	FUJIYAKUHIN Co., Ltd.	May 25, 2020
Cabozantinib malate Cabometyx tablets 20 mg, 60 mg	Takeda Pharmaceutical Company Limited.	May 22, 2020
Borofalan (^{10}B) Steboronine 9000 mg/300 mL for infusion	STELLA PHARMA CORPORATION	May 20, 2020
Tirabrutinib hydrochloride Velexbru Tablets 80 mg	Ono Pharmaceutical Co., Ltd.	May 20, 2020
Viltolarsen Viltepso Injection 250 mg	Nippon Shinyaku Co., Ltd.	May 20, 2020
Sodium zirconium cyclosilicate hydrate Lokelma 5 g/10 g powder for suspension (single-dose package)	AstraZeneca K.K.	May 20, 2020
Remdesivir Veklury for Intravenous Injection 100 mg	Gilead Sciences Inc.	May 11, 2020
Upadacitinib hydrate Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	April 24, 2020
Posaconazole Noxafil Tablets 100 mg	MSD K.K.	April 24, 2020
Lurasidone hydrochloride Latuda tablets 20 mg, 40 mg, 60 mg, 80 mg	Sumitomo Dainippon Pharma Co., Ltd.	April 22, 2020
Dinoprostone Propess vaginal inserts 10 mg	Ferring Pharmaceuticals Co., Ltd.	April 2, 2020
Mepolizumab (genetical recombination) Nucala for s.c. injection 100 mg	Glaxo Smith Kline K.K.	March 25, 2020
Dupilumab (genetical recombination) *4 Dupixent 300 mg Syringe for S.C. Injection	Sanofi K.K.	March 25, 2020
pH4-Treated normal human immunoglobulin*5 Privigen 10% I.V. Drip Infusion 5g/50mL, 10g/100mL, 20g/200mL	CSL Behring K.K.	February 21, 2020
Entrectinib*6 Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	February 21, 2020
Modafinil*7 Modiodal Tablets 100 mg	Alfresa Pharma Corporation	February 21, 2020
Doravirine Pifeltro Tablets 100 mg	MSD K.K.	February 17, 2020
Insulin aspart (genetical recombination) Fiasp Injection FlexTouch, Fiasp Injection Penfill, Fiasp Injection 100 U/mL	Novo Nordisk Pharma Ltd.	February 7, 2020
Dolutegravir sodium/lamivudine Dovato combination tablets	Viiv Healthcare K.K.	January 31, 2020

Nonproprietary name Branded name on		Name of the MAH	Date of EPPV initiate
	Freeze-dried recombinant herpes zoster vaccine (prepared from Chinese hamster ovary cells) Shingrix for intramuscular injection	Glaxo Smith Kline K.K.	January 29, 2020
	Turoctocog alfa pegol (genetical recombination) Esperoct for i.v. injection 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	January 29, 2020
	Perampanel hydrate*8 Fycompa tablets 2 mg, 4 mg	Eisai Co., Ltd.	January 23, 2020
	Lascufloxacin hydrochloride Lasvic Tablets 75 mg	Kyorin Pharmaceutical Co.,Ltd.	January 8, 2020

*1 Improvement of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

*2 Tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) associated with sepsis

*3 Progressive fibrosing interstitial lung disease

*4 Chronic rhinosinusitis with nasal polyps (only in patients not adequately controlled with existing therapies)

*5 Agammaglobulinemia or hypogammaglobulinemia

*6 ROS1 fusion-positive, unresectable, advanced or metastatic non-small cell lung cancer

*7 Excessive daytime sleepiness associated with idiopathic hypersomnia

*8 Partial-onset seizures (including secondarily generalized seizures)