Pharmaceuticals and Medical Devices Safety Information

No. 302 June 2013

Table of Contents

This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on 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) website (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

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Pharmaceuticals and Medical Devices Safety Information
No. 302 June 2013

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

[Outline of Information]

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

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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

ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
ALP	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
APTT	Activated partial thromboplastin time
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
BALF	Bronchoalveolar lavage fluid
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CHDF	Continuous hemodiafiltration
CO_2	Carbon dioxide
CRP	C-reactive protein
CRT-D	Cardiac resynchronization therapy defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
CT	Computed tomography
DMARD	Disease-modifying antirheumatic drug
EAS	Electronic article surveillance
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
EV/PHV	Electric vehicle/Plug-in hybrid vehicle
FFP	Fresh frozen plasma
GCS	Glasgow come scale
Hb	Hemoglobin
HHV-6	Human herpesvirus 6
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
IH	Induction heating
IPG	Implantable pulse generator
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PLT	Platelet
PT	Prothrombin time
PT-INR	Prothrombin time - international normalized ratio
RA	Rheumatoid arthritis
RBC	Red blood cell count
SLE	Systemic lupus erythematosus
SP-D	Surfactant protein D
SpO_2	Oxygen saturation
TEN	Toxic epidermal necrolysis
WBC	White blood cell count
γ-GTP	gamma-glutamyl transpeptidase

1

Severe Haemorrhages Associated with Suspected Interaction between Antirheumatic Iguratimod and Warfarin

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Iguratimod	Careram Tablets 25 mg (Eisai Co., Ltd.) KOLBET Tablets 25 mg (Toyama Chemical Co., Ltd.)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous	
Indications	Rheumatoid arthritis	

1. Introduction

Iguratimod (Careram Tablets 25 mg and KOLBET Tablets 25 mg; hereafter "iguratimod") has a chromone structure and is a disease-modifying antirheumatic drug (DMARD) that inhibits production of immunoglobulin and inflammatory cytokine. In Japan, iguratimod was approved for the treatment of rheumatoid arthritis in June 2012.

In the data from a pharmacodynamic drug interaction study in rats submitted for approval review of iguratimod, an iguratimod dose-dependent increase of prolongation of prothrombin time (PT) and activated thromboplastin time (APTT) caused by warfarin was found when iguratimod was administered with warfarin, and a precaution against the concomitant use of iguratimod with warfarin has been included in the package insert since approval[1)].

Based on the reported 3 cases (2 serious cases and 1 non-serious case) of haemorrhagic event and/or increased prothrombin time/international normalized ratio (PT/INR) associated with the concomitant use of iguratimod and warfarin by December 2012 in Japan, the marketing authorization holders (MAHs) of iguratimod alerted healthcare professionals and patients about the drug interaction by distributing information materials for them[2)3)].

In May 2013, a fatal case of pulmonary alveolar haemorrhage associated with a suspected interaction between iguratimod and warfarin was reported. MHLW instructed the MAHs of iguratimod to contraindicate the concomitant use of iguratimod with warfarin and to distribute the Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter)[4)] on May 17, 2013 because (1) the patient in this case died of pulmonary alveolar haemorrhage despite periodic blood coagulation tests given in accordance with the precaution issued in December 2012, (2) the frequency of haemorrhagic events and elevated PT/INR may be increased in patients concurrently treated with iguratimod and warfarin, and (3) the contraindication for concomitant use will not greatly affect clinical practice since alternative drugs to iguratimod are available.

The mechanism of iguratimod-warfarin interaction is yet to be identified. PMDA continuously works with MAHs to identify the mechanism.

2. Incidence of haemorrhagic events and increased PT/INR associated with suspected interaction between iguratimod and warfarin

According to the interview survey conducted by MAHs of iguratimod after the issuance of the Blue Letter, iguratimod has been used in 2879 cases as of May 15, 2013 since the initial marketing on September 12, 2012, and 42 cases of them were concurrently using warfarin. Haemorrhagic events and

elevated PT-INR were reported by 12 (3 of them were identified to be serious, including 1 fatal case) of the 42 cases, showing at a high frequency (28.6%).

A line list of the 12 cases with haemorrhagic events and/or elevated PT-INR and the clinical course of the fatal case are presented below.

Cases where haemorrhage and abnormal coagulation test results were found in patients treated with iguratimod and warfarin

Case No.	Sex	Age	Adverse reactions	Seriousness	Daily dose	Latency time to onset of adverse reactions	Treatment by iguratimod	Outcome
1	F	70s	Increased PT-INR Pulmonary alveolar haemorrhage	Serious	50 mg	12 days 41 days	Discontinuation	Recovered (Increased PT-INR) Death (Pulmonary alveolar haemorrhage)
2	F	60s	Positive occult blood Gingival bleeding Subcutaneous bleeding Anaemia	Serious	25 mg	23 days 12 days 14 days 23 days	Discontinuation	Unknown (positive occult blood) Recovered (Gingival bleeding) Recovered (Subcutaneous bleeding) Recovered (Anaemia)
3	M	80s	Puncture site haemorrhage Conjunctival haemorrhage	Serious	25 mg	29 days 29 days	Discontinuation	Recovered (Puncture site haemorrhage) Recovered (Conjunctival haemorrhage)
4	F	70s	Increased PT-INR	Non-serious	25 mg	28 days	Discontinuation	Unknown
5	F	70s	Increased PT-INR	Non-serious	25 mg	28 days	Continuation	Recovered
6	F	60s	Increased PT-INR	Non-serious	25 mg	Unknown	Unknown	Unknown
7	F	50s	Increased PT-INR	Non-serious	25 mg	14 days	Continuation	Recovered
8	F	60s	Subcutaneous bleeding	Non-serious	50 mg	109 days	Discontinuation	Recovered
9	M	60s	Haematoma	Non-serious	25 mg	15 days	Discontinuation	Recovered
10	F	60s	Epistaxis	Non-serious	50 mg	43 days	Continuation	Recovered
11	F	80s	Increased PT-INR	Non-serious	50 mg	45 days	Discontinuation	Recovered
12	M	60s	Subcutaneous bleeding	Non-serious	50 mg	60 days	Discontinuation	Recovered

Case Summary

Patient		Daily dose/ Treatment duration	Adverse reactions
Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures

Female 70s	Rheumatoid arthritis (atrial fibrillation) (interstitial lung disease) (chronic bronchitis) (insomnia) (depression) (osteoporosis) (renal impairment)	25 mg for 31 days 50 mg for 10 days	**Increased PT-INR, pulmonary alveolar haemorrhage** Approximately 16 years before administration: Rheumatoid arthritis (RA) developed. Approximately 6 years before administration: Administration of warfarin potassium (3 mg/day) was started. 6 days before administration: A laboratory test result showed PT/INR 1.34 under administration of warfarin potassium (2.5 mg/day). Day 1 of administration: Iguratimod (25 mg/day) was added to existing treatment because treatment with salazosulfapyridine, tacrolimus hydrate, and prednisolone could not control RA. Day 2 of administration: PT/INR 1.35 Day 12 of administration: PT/INR increased to 2.94. Day 18 of administration: The dose of warfarin potassium was reduced to 2.0 mg/day. Day 22 of administration: PT/INR 2.29 Day 32 of administration: The dose of iguratimod was increased to 50 mg/day. Day 41 of administration: Pulmonary alveolar haemorrhage occurred. The patient felt shortness of breath and dyspnoea. Day 42 of administration (day of discontinuation): Administration of igratimod was discontinued without consulting her healthcare professionals. 1 day after discontinuation: Oxygen saturation (SpO_2) was in the range of 80%. PT/INR 7.18. A chest computed tomography (CT) showed new ground-glass opacities in addition to an increased contrast of existing shadows. The patient was diagnosed with pulmonary alveolar haemorrhage based on altered color and detection of hemosiderin-laden macrophages in the bronchoalveolar lavage fluid (BALF). The patient was admitted to hospital. Pulse therapy with methylprednisolone (500 mg) was carried out. Administration of tazobactam sodium/piperacillin sodium and sulfamethoxazole/trimethoprim (4 tablets) was started. 2 days after discontinuation: PT/INR 11.91. Administration of 4U of fresh frozen plasma (FFP), injectable menatetrenone (10 mg), and oral menatetrenone (45 mg/day) was started. 3 days after discontinuation: Haemorrhage was successfully controlled, with rapid improvement in PT/INR to 1.24. Because her breathing difficulty worsened, administration of morphine was started. Because pneumocystis polymerase chain reaction (PCR) result was negative and β-D-glucan level was negative, a dose of sulfamethoxazole/trimethoprim was reduced to preventive dosage. SpO_2 was 95% with a reservoir mask of 15 L/min O_2. After 3 days after discontinuation: Arterial oxygenation did not improve. Respiratory depression by morphine occurred. 13 days after discontinuation: The patient died.
Concomitant medications: warfarin potassium, salazosulfapyridine, prednisolone, tacrolimus hydrate, teprenone, sulindac, zolpidem tartrate, sodium risedronate hydrate			

Laboratory Examination

Parameters	6 days before admin-istration	Day 2 of admin-istration	Day 12 of admin-istration	Day 22 of admin-istration	Day 29 of admin-istration	1 day after discontin-uation	2 days after discontin-uation	3 days after discontin-uation	5 days after discontin-uation	6 days after discontin-uation	9 days after discontin-uation
PT-INR	1.34	1.35	2.94	2.29	2.27	7.18	11.91	1.24	3.06	1.32	1.17
RBC ($\times 10^4/\mu L$)	382	-	363	-	385	381	325	319	306	-	304
HB (g/dL)	11.0	-	10.5	-	10.8	10.6	9.1	8.7	8.3	-	8.2

3. Conclusion

Healthcare professionals are reminded of the following recommendations:

(1) For patients who are taking iguratimod concomitantly with warfarin, discontinuation of iguratimod should be considered.

(2) Iguratimod should not be administered to patients who are required to receive warfarin therapy.

See "3. Important Safety Information" on page 21 for the package insert revised in line with the issuance of the Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) to the MAHs.

Aside from the interaction with warfarin, iguratimod may cause a variety of adverse reactions. Healthcare professionals are encouraged to cooperate the proper use of iguratimod based on a thorough understanding of its safety profile.

<References> (including provisionally translated titles)

1) Careram Tablets 25 mg/KOLBET Tablets 25 mg Review Report dated April 27, 2012 (only available in Japanese language)
http://www.info.pmda.go.jp/shinyaku/P201200067/480297000_22400AMX00731000_A100_1.pdf

2) Careram Tablets; precaution against concomitant use with warfarin (only available in Japanese language)
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201212_1.pdf

3) KOLBET Tablets; precaution against concomitant use with warfarin (only available in Japanese language)
http://www.info.pmda.go.jp/iyaku_info/file/kigyo_oshirase_201212_2.pdf

4) Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter): Careram Tablets 25 mg; KOLBET Tablets 25 mg (iguratimod) -Risk of severe haemorrhages by a interaction with warfarin
http://www.pmda.go.jp/english/service/pdf/letter/130517-iguratimod.pdf

2

Revision of Precautions for the Effect of Battery Chargers for Electric Cars on Implantable Cardiac Pacemakers

1. Introduction

Electric cars and plug-in hybrid cars*1 (hereafter collectively referred to as "electric cars") with excellent energy efficiency and low CO_2 emissions have been introduced in the automobile market in light of increasing energy constraints and measures against global warming. Charging points are increasingly being set up with the expansion of electric car use. Two types of electric chargers are available. One is an ordinary battery charger to be used/placed at home, the office, and other private areas where electric cars may be parked for a relatively long time. This type needs 8-14 hours for electric charging. And the other is a quick charger for rapid electric charging usually placed in highway service areas and other public places, such as gas stations[1)].

The effect of electromagnetic waves from mobile phones, electric article surveillance (EAS) systems, and induction heating (IH) home appliances on implantable medical devices such as implantable cardiac pacemakers have been evaluated, and precaution has been raised against their adverse effects in the past. And recently, a verification test was performed to evaluate the effect of electromagnetic waves from battery chargers for electric cars on implantable cardiac pacemakers, etc. Based on the test results, the Precautions section of package inserts of implantable cardiac pacemakers was revised to raise caution for patients and healthcare professionals.

*1 Plug-in hybrid cars: hybrid cars with batteries that can be charged from external power sources, and have the advantage of electric cars and hybrid cars that can go a long distance with gasoline engines and motors.

2. Overview of verification test

(1) Testing institutions

1) Test of quick chargers
CHAdeMO Association
Japan Arrhythmia Device Industry Association

2) Test of ordinary battery chargers
Electric Vehicle Power Supply System Association
Japan Automobile Research Institute
Japan Arrhythmia Device Industry Association
Wireless Technologies & EMC Research Laboratories, Graduate School of Information Science and Technology, Hokkaido University

(2) Testing equipment

Test devices included implantable pulse generator (IPG), implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy defibrillator (CRT-D), and cardiac resynchronization therapy pacemaker (CRT-P). Twenty-five models of 5 MAHs (13 IPGs and CRT-Ps of 5 MAHs, 12 ICDs and CRT-Ds of 5 MAHs) were selected as the test devices. The sensitivity of each implantable medical

device was set at the maximum. The program and operating status, including the sensitivity, of the devices were set in accordance with "Study report on the effects of electromagnetic waves on medical devices" published by the Ministry of Internal Affairs and Communications[2)].

Test battery chargers included a Mode-2 ordinary charger*[2], a Mode-3 ordinary charger*[3], and a quick charger. An electronic load was used to simulate a charging status with the maximum charging current.

The ordinary battery chargers were also tested under forced interruption during charging. (Note that it was an exaggerated simulation of cardiac cycle synchronization; forced interruption is not expected under the normal use.)

*2 A Mode 2 ordinary charger has a built-in communication control unit inside the cable.
*3 A Mode 3 ordinary charger has a built-in communication control unit inside the charger. Mode 1 ordinary chargers are not available in Japan.

(3) Testing methods

After setting an implantable medical device in a humanoid phantom*[4], a battery charger was pressed against the phantom to evaluate the effect of the electromagnetic waves from the charger on the medical device as shown in Table 1. If the medical device was affected in any way, the charger was incrementally moved away from the phantom by a certain distance, and the minimum distance with which the effect disappeared (maximum no interference distance) was documented. The charger was held at the distance for 30 seconds to see if the medical device was affected as shown in Table 1.

The test result was documented as "affected" when the reproducibility of the effect of the charger was confirmed under the test conditions or when any change of the set value or unexpected change of the device conditions under normal circumstances was noted by the device inspection after the test.

The measuring device used for the test was set up in accordance with "Study report on the effects of electromagnetic waves on medical devices" published by the Ministry of Internal Affairs and Communications.

*4 Humanoid phantom: A tub filled with 0.18% by weight saline used to reproduce electric currents induced in a human body by decreased magnetic field or electromagnetic interference

Table 1 Test conditions and evaluation of the effect on implantable medical devices

Test conditions		Assessment of the effect on implantable medical device
Inhibition test	With the implantable medical device pulsing at the set rate with no signal input	Inhibition of pulsing of the implantable medical device or change of pulsing interval
Asynchronous test	With the implantable medical device sensing a simulated potential signal at 10% to 20% higher than the set rate and the output pulse inhibited; the amplitude of the simulated potential signal was set at about twice the minimum amplitude to which the device responded	Pulse generation from the implantable medical device
False positive test*[5] (performed when the device was affected in the inhibition test or the asynchronous test)	Confirmation of fibrillation detection under the conditions used in the inhibition test and the asynchronous test; the same test conditions used	False detection of fibrillation in the implantable medical device
False negative test*[5] (not performed when the device was affected in the false positive test)	With simulated signal within the fibrillation detection cycle used in the inhibition test and the asynchronous test	Failure of fibrillation detection by implantable medical device

*5 For ICDs and CRT-Ds only

(4) Test results

The quick and ordinary battery chargers inhibited the pacing pulse and induced the asynchronous pacing pulse in the IPGs and CRT-Ps. On the other hand, the ICDs and CRT-Ds were not affected by the chargers.

The IPG and CRT-P test results are summarized below.

1) Effect of the quick charger on the IPGs and CRT-Ps

Twelve models were affected by the charger when used with the monopolar setting, but none was affected when used with the bipolar setting. The observed effect was reversible; it disappeared as the charger was moved away. The maximum no interference distance was 53 cm. The model with which the maximum no interference distance was documented was still affected by the charger when its sensitivity was set a level lower from the maximum sensitivity under the same test conditions.

2) Effect of ordinary battery charger on the IPGs and CRT-Ps

The devices were affected by both Mode 2 and Mode 3 ordinary chargers. Up to 10 models were affected when used with the monopolar setting. Two models were affected by the Mode 2 ordinary charger when used with the bipolar setting. The effect of ordinary battery chargers was only seen when the sensitivity was set at the maximum. The effect was also reversible; it disappeared as the charger was moved away. The maximum no interference distance was 12.5 cm.

Table 2 Models affected by electromagnetic waves*[6]

Electrode polarity of IPG and CRT-P / Charger type	Monopolar*[7]	Bipolar*[7]
Quick charger	12 models	-*[8]
Mode 2 ordinary charger	10 models	2 models
Mode 3 ordinary charger	10 models	-

*6 "-" in the above table refers to no device affected by electromagnetic waves; same in Table 3
*7 Of the 13 models tested, 1 model of them had only a bipolar setting; same in Table 3
*8 The bipolar setting was used in 5 models tested with the quick charger. The model of each of the 5 MAHs showing the maximum no interference distance in the monopolar setting test was selected; same in Table 3

Table 3 Maximum no interference distance*[9]

Electrode polarity of IPG and CRT-P / Charger type	Monopolar	Bipolar
Quick charger	53 cm	-
Mode 2 ordinary charger	12.5 cm	5 cm
Mode 3 ordinary charger	7.5 cm	-

*9 Of the maximum no interference distance documented under each test condition (including "charging status with steady current" and "sudden charge disruption" for the ordinary battery chargers), the maximum date is shown in the table.

3. Safety measures

The verification test showed the IPGs and CRT-Ps were affected by the quick and ordinary battery chargers. The maximum no interference distance was 53 cm for the quick charger and 12.5 cm for the ordinary battery charger. Patients who have implanted IPG and CRT-P may be able to avoid the adverse effect of electromagnetic waves by staying away from quick chargers and avoiding handling them as much as possible, and when handling ordinary battery chargers, avoiding a position in which chargers and charging cables are pressed against their bodies. The adverse effects of quick and ordinary battery chargers are reversible. Even if the patient accidentally goes close to a quick charger or has a ordinary battery charger pressed against his body, he may be able to avoid the risk of adverse effects by promptly walking away from the quick charger or moving the ordinary battery charger away from his body.

MHLW has instructed the MAHs of IPGs and CRT-Ps to include the following descriptions in the Precautions section of the package insert to raise caution about the adverse effects of battery chargers for electric car and to warn patients using the devices by including supplemental precautions in the patient notebook and distributing information brochures[3)].

○ IPG and CRT-P package insert
Descriptions to be included under the heading, "Precautions concerning home appliances and the environment" in "Important Precautions" in the Precautions section

> Battery chargers for electric cars (including plug-in hybrid cars) may temporarily influence the pacing output of this product. Patients should be instructed to pay attention to the following points.
>
> (1) Patients should not use quick chargers for electric cars.
> (2) Patients should stay away from places where a quick charger is installed as much as possible. If patients carelessly get near to such a place, they should leave the place quickly without pausing.
> (3) If patients use an ordinary battery charger for electric cars, they should not assume a position where they may get close to the charging station or charging cable during charging.

In cooperation with the Ministry of Economy, Trade and Industry and the Ministry of Land, Infrastructure, Transport and Tourism, MHLW has requested the MAHs and distributors of electric cars and chargers to thoroughly inform consumers of the adverse effect of IPGs and CRT-Ps in the users' manuals, etc. and to attach warning stickers on chargers in a clearly visible manner to help patients identify the risk on the street.

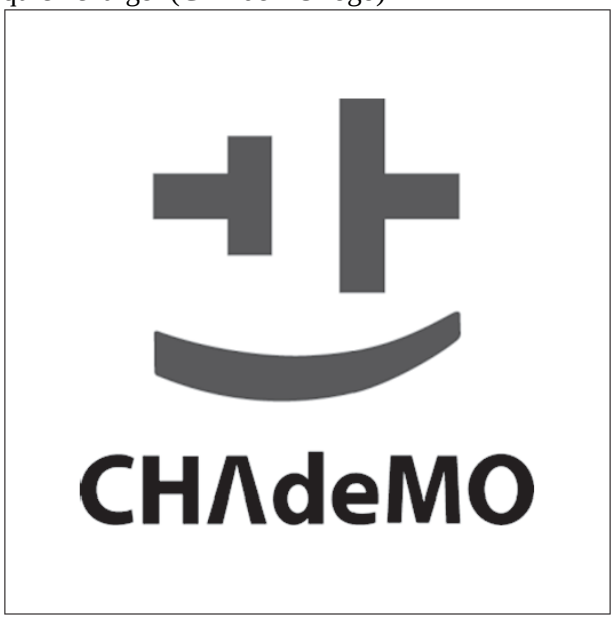
4. Conclusion

Healthcare professionals are advised to warn your patients that battery chargers for electric cars may temporarily affect the pacing output of IPGs and CRT-Ps and raise caution about handling ordinary and quick (battery) chargers. Ordinary battery chargers (to be placed in public areas where patients will have access in general) and quick chargers have been attached specific stickers (logos of the CHAdeMO Association and the Electric Vehicle Power Supply System Association) on their exterior. Let your patients know about the stickers to help them recognize and distinguish the chargers.

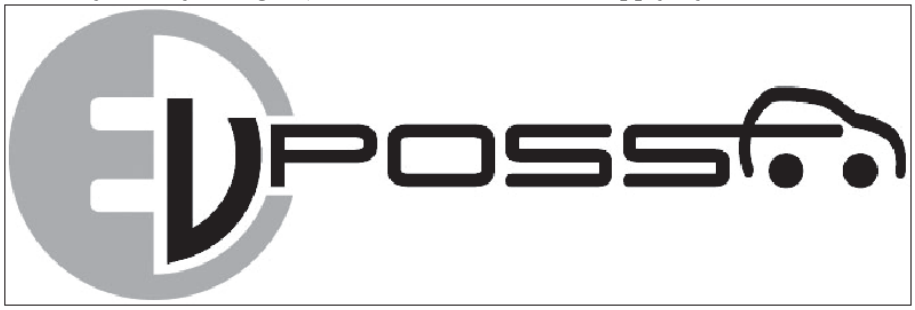
A patient leaflet including a caution against the use of electric car chargers and precautions to be used in daily life is prepared by the Japan Arrhythmia Device Industry Association and are available from the Japan Arrhythmia Device Industry Association website for downloading. Please utilize the information and materials (http://www.jadia.or.jp/images/poster/ wide/2013.pdf).

<Stickers on chargers>

quick charger (CHAdeMO logo)



Ordinary battery charger (Electric Vehicle Power Supply System Association logo)



<References> (including provisionally translated titles)

1) Ministry of Economy, Trade and Industry website (EV/PHV platform and charging facilities)
http://www.meti.go.jp/policy/automobile/evphv/what/charge/index.html
2) Ministry of Internal Affairs and Communications "Study report on the effects of electromagnetic waves on medical devices", March 2012
http://www.tele.soumu.go.jp/resource/j/ele/seitai/h23.pdf
3) Joint PFSB/SD Notification No. 0319-3 and PFSB/ELD/OMDE Notification No. 0319-1, by the Director of Safety Division, Pharmaceutical and Food Safety Bureau and by the Director of Office of Medical Devices, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 19, 2013, "Revision of Precautions for the Effect of Battery Chargers for Electric Cars on Implantable Cardiac Pacemakers" (only available in Japanese language)
http://www.info.pmda.go.jp/mdevices/file/md2013-0319001.pdf

See the past articles on the adverse effects of electromagnetic waves from various types of equipment on implantable cardiac pacemakers which appeared in the Pharmaceuticals and Medical Devices Safety Information on the URLs listed below.

1) Pharmaceuticals and Medical Devices Safety Information No.155 "Effects of anti-shoplifting devices and metal detectors on implantable cardiac pacemakers, implantable defibrillators, and cerebral/spinal cord stimulators" (only available in Japanese language)

http://www1.mhlw.go.jp/houdou/1106/h0630-1_a_15.html#3
2) Pharmaceuticals and Medical Devices Safety Information No.173 “Effects of antitheft devices and metal detectors on implantable cardiac pacemakers, implantable defibrillators, and cerebral/spinal cord stimulators (pacemakers)” (only available in Japanese language)
http://www.mhlw.go.jp/houdou/2002/01/h0117-3a.html#13
3) Pharmaceuticals and Medical Devices Safety Information No.179 “Guidelines for the use of mobile phones to prevent adverse effects of electromagnetic waves on medical devices” (only available in Japanese language)
http://www.mhlw.go.jp/houdou/2002/07/h0725-1.html
4) Pharmaceuticals and Medical Devices Safety Information No.190 “Effects of electromagnetic waves from wireless card systems on implantable medical devices (cardiac pacemakers and cardioverter defibrillators)” (only available in Japanese language)
http://www.mhlw.go.jp/houdou/2003/06/h0626-1.html
5) Pharmaceuticals and Medical Devices Safety Information No.203 “Effects of electromagnetic waves from antitheft devices, etc. on medical devices”
http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-203.pdf
6) Pharmaceuticals and Medical Devices Safety Information No.216 “Effects on implantable medical devices (cardiac pacemakers and cardioverter defibrillators) by new system mobile phone terminals and RFID devices”
http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-216.pdf
7) Pharmaceuticals and Medical Devices Safety Information No.226 “Effects on implantable medical devices (cardiac pacemakers and cardioverter defibrillators) by new system mobile phone terminals”
http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-226.pdf
8) Pharmaceuticals and Medical Devices Safety Information No.237 “The effect from RFID devices in UHF band and mobile phone terminals with a new system on implantable medical devices such as cardiac pacemakers etc”
http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-237.pdf

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notifications dated April 23 and May 17, 2013, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Ambrisentan

Brand Name (name of company)	Volibris Tablets 2.5 mg (GlaxoSmithKline K.K.)
Therapeutic Category	Cardiovascular agents-Miscellaneous
Indications	Pulmonary arterial hypertension

PRECAUTIONS (underlined parts are revised)

Careful Administration

Patients with interstitial pneumonia

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur or be aggravated. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If the onset or aggravation of interstitial pneumonia is suspected after administration of this drug, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 2 years and 6 months (from initial marketing to March 18, 2013)

- Interstitial pneumonia: 2 cases (no fatal cases)

The number of patients using this drug estimated by MAHs: Approximately 1,486 (September 2012 to November 2012)
Launched in Japan: September 2010

Case Summaries

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 50s	Secondary pulmonary arterial hypertension (collagen disorder, interstitial pneumonia, overlap	5 mg for 58 days	**Aggravated interstitial pneumonia, increased white blood cell** Day 1 of administration: The patient started receiving ambrisentan at 5 mg. White blood cell (WBC), 4050/μL; KL-6, 601 U/mL; SpO_2, 94% (O_2/L). Day 16 of administration: KL-6 was slightly elevated to 726 U/mL. Day 30 of administration: WBC did not decrease (5380/μL). Chest CT showed new ground-glass opacities in the left S3

		syndrome, osteoporosis, iron deficiency anaemia, chronic gastritis, insomnia)		peripheral region and left S8. SpO_2 was 92%. Interstitial pneumonia became aggravated. Day 58 of administration (day of discontinuation): WBC decreased to 3240/μL. KL-6 increased to 1033 U/mL. This event was suspected to be drug-induced, and administration of ambrisentan was discontinued. SpO_2 was 93%. White blood cell decreased. 27 days after discontinuation: WBC increased to 5520/μL. KL-6 slightly decreased to 945 U/mL. The ground-glass opacities in the left S3 and left S8 on the chest CT disappeared. SpO_2 was 95%. Aggravated interstitial pneumonia and leucopenia resolved. 56 days after discontinuation: KL-6 decreased to 773 U/mL. SpO_2 was 95%.
	Concomitant medications: tadalafil, warfarin potassium, prednisolone, famotidine, alendronate sodium hydrate, teprenone, brotizolam, etizolam, sulpiride, sodium ferrous citrate			

Laboratory Examination

	Day 1 of administration	Day 16 of administration	Day 30 of administration	Day 58 of administration (day of discontinuation)	27 days after discontinuation	56 days after discontinuation
WBC (/μL)	4,050	-	5,380	3,240	5,520	-
KL-6 (U/mL)	601	726	-	1,033	945	773

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 30s	Pulmonary arterial hypertension (systemic lupus erythematosus, interstitial pneumonia, pancytopenia, pericardial effusion, Hashimoto's disease)	2.5 mg for 13 days	**Interstitial pneumonia (aggravated), shortness of breath on exercise, decreased arterial oxygen saturation** Approximately 1.5 months before administration: The patient started receiving prednisolone 60 mg as overall treatment for systemic lupus erythematosus (SLE). She also started receiving tadalafil 40 mg for treatment of pulmonary hypertension. Day 1 of administration: Administration of ambrisentan 2.5 mg was started because pulmonary arterial pressure tended to improve but remained elevated. Day 3 of administration: The patient complained of shortness of breath when exercising. SpO_2 decreased. Day 9 of administration: Although echocardiography did not show any findings of heart strain, chest CT showed aggravation of interstitial pneumonia. Day 13 of administration (day of discontinuation): This event was considered as an adverse reaction to ambrisentan; dosage of other drugs was unchanged, while administration of ambrisentan was discontinued. 2 days after discontinuation: Shortness of breath was relieved with improvement in SpO_2.

				6 days after discontinuation: Chest CT showed that interstitial pneumonia appeared to improve. Since then, there have been no findings suggestive of aggravation of interstitial pneumonia. Her symptom of shortness of breath resolved.
	Concomitant medications: tadalafil, levothyroxine sodium hydrate, alfacalcidol, mosapride citrate hydrate, prednisolone sodium succinate			

Laboratory Examination

	48 days before admin-istration	28 days before admin-istration	7 days before admin-istration	Day 4 of admin-istration	Day 9 of admin-istration	Day 11 of ad-ministra-tion	2 days after discontin-uation	5 days after discontin-uation	9 days after discontin-uation	16 days after discontin-uation
SP-D (ng/mL)	-	103	-	-	-	225	-	-	117	80.2
KL-6 (U/mL)	440	-	-	-	-	332	-	-	419	341
LDH (IU/L)	-	-	231	274	-	278	-	216	-	-
CRP (mg/dL)	-	-	< 0.3	0.3	0.8	-	< 0.3	-	-	-

2 Tranexamic Acid

[1] Tranexamic Acid (oral dosage form)

Brand Name (name of company)	TRANSAMIN TABLETS 250 mg, 500 mg, TRANSAMIN CAPSULES 250 mg, TRANSAMIN POWDER 50% (Daiichi Sankyo Company, Limited), TRANSAMIN SYRUP 5% (Nipro Patch Co., Ltd.), and the others
Therapeutic Category	Hemostatics
Indications	○ Bleeding tendency probably induced by increased systemic fibrinolysis (leukaemia, aplastic anaemia, purpura, etc., and intra/postoperative abnormal haemorrhage) ○ Abnormal haemorrhage probably induced by increased local fibrinolysis (pulmonary haemorrhage, epistaxis, genital haemorrhage, renal haemorrhage, abnormal haemorrhage during and after prostatic operation) ○ Symptoms such as erythema, swelling, and itching in the following diseases: Eczema and similar diseases, urticaria, drug eruption, toxicoderma ○ Symptoms such as pharynx pain, redness, hyperaemia, and swelling in the following diseases: Tonsillitis, laryngopharyngitis ○ Oral pain and aphtha associated with stomatitis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Convulsion: Convulsion may occur in hemodialysis patients. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

[2] Tranexamic Acid (injectable dosage form)

Brand Name (name of company)	TRANSAMIN INJECTION 5%, 10% (Daiichi Sankyo Company, Limited), and the others
Therapeutic Category	Hemostatics
Indications	○ Bleeding tendency probably induced by increased systemic fibrinolysis (leukaemia, aplastic anaemia, purpura, etc., and intra/postoperative abnormal haemorrhage) ○ Abnormal haemorrhage probably induced by increased local fibrinolysis (pulmonary haemorrhage, epistaxis, genital haemorrhage, renal haemorrhage, abnormal haemorrhage during and after prostatic operation) ○ Symptoms such as erythema, swelling, and itching in the following diseases: Eczema and similar diseases, urticaria, drug eruption, toxicoderma ○ Symptoms such as pharynx pain, redness, hyperaemia, and swelling in the following diseases: Tonsillitis, laryngopharyngitis ○ Oral pain and aphtha associated with stomatitis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Convulsion: Convulsion may occur after cardiovascular surgery using a cardiopulmonary bypass in patients receiving this drug in the perioperative period. Convulsion has also been reported in hemodialysis patients. Patients should be carefully monitored and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 4 years (April 1, 2009 to March 14, 2013)

- Convulsion-associated cases: 23 cases (no fatal cases)

The number of patients using this drug estimated by MAHs:
(Tablets, capsules, powder): Approximately 20.34 million (August 2011 to August 2012)
(Injection): Approximately 2.39 million (August 2011 to August 2012)
(Syrup): Approximately 1.34 million (September 2011 to August 2012)
Launched in Japan: September 2002 (injection 5%, 10%, tablets 250 mg)
September 1981 (tablets 500 mg)
October 1965 (capsules 250 mg)
August 2002 (powder 50%)
September 1966 (syrup 5%)

Case Summaries [oral and injectable dosage forms]

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Acute pharyngitis, ultrafiltration failure in Continuous ambulatory peritoneal dialysis (CAPD), melaena (hepatitis C, diabetic renal	(oral dosage form) 1,500 mg for 4 days (oral dosage form) 1,500 mg for 3 days	**Convulsion** 13 days before administration: The patient was admitted to hospital due to diabetic renal failure. Day 1 of administration: Tranexamic acid 1,500 mg, loxoprofen sodium (as anhydride) 180 mg, and 3 tablets of cefcapene pivoxil hydrochloride hydrate were administered for acute pharyngitis. Day 3 of administration: Peritoneal dialysis therapy was started. Poor ultrafiltration then persisted.

		failure, diabetes mellitus, intracranial haemorrhage, left femoral fracture, haemodialysis)	(injectable dosage form) 2 g for 4 days	Day 4 of administration (day of completion): Administration of tranexamic acid was terminated. 1 day after completion: Convulsion of the face and both upper limbs developed, and administration of tranexamic acid was discontinued. Diazepam was administered. 5 days after completion: Symptoms resolved. 53 days after completion: Haemodialysis was started (until 66 days after termination). 93 days after completion: Intracranial haemorrhage and left femoral fracture due to fall were found, for which administration of tranexamic acid was not administered. 96 days after completion: Haemodialysis was started (until 22 days after discontinuation of readministration). 104 days after completion (Day 1 of readministration): Tranexamic acid was administered at 1,500 mg for poor ultrafiltration in CAPD because tranexamic acid has been reported to be effective. Day 2 of readministration: Generalised convulsion and consciousness clouding occurred. Day 3 of readministration (day of discontinuation of readministration): Administration of tranexamic acid was discontinued. Phenobarbital and phenytoin were administered. 2 days after discontinuation of readministration: Symptoms were resolved. 24 days after discontinuation of readministration (day of re-readministration): Drip infusions of carbazochrome sodium sulfonate hydrate 100 mg and tranexamic acid 2 g were given for melaena. Day 3 of re-readministration: Generalised convulsion and consciousness clouding were found. Phenytoin was intravenously administered. Day 4 of re-readministration (day of discontinuation of re-readministration): Administration of tranexamic acid was discontinued. Phenytoin injection and diazepam were administered. 2 days after discontinuation of re-readministration: Haemodialysis was started. Phenobarbital was administered. 3 days after discontinuation of re-readministration: Symptoms were resolved.
	Concomitant medications: loxoprofen sodium hydrate, cefcapene pivoxil hydrochloride hydrate, carbazochrome sodium sulfonate hydrate, physiological saline solution			

Laboratory Examination

	2 days before administration	1 day after completion	11 days after completion	100 days after completion	2 days after discontinuation of readministration	8 days after discontinuation of readministration	22 days after discontinuation of readministration	3 days after discontinuation of re-readministration
WBC (/μL)	3,940	8,330	4,380	7,630	13,230	10,420	8,170	17,560
RBC ($\times 10^4$/μL)	274	305	287	336	275	246	227	282
Hemoglobin (g/dL)	8.4	9.4	8.9	10.4	8.6	7.5	6.9	8.6

Hematocrit (%)	26.6	29.8	27.6	31.2	21.6	23.1	21.8	26.3
PLT ($\times 10^4/\mu L$)	19.5	19.5	12.5	17.6	26.4	24.2	36.3	27.0
BUN (mg/dL)	41.9	45.2	32.1	60.7	60.9	62.2	42.0	49.9
Blood creatinine (mg/dL)	4.68	5.25	6.14	8.21	7.53	7.02	6.78	5.51
Serum potassium (mEq/L)	5.1	4.4	3.3	4.1	4.5	6.4	4.1	3.8
Serum sodium (mEq/L)	141	132	135	135	135	127	128	131
Serum calcium (mg/dL)	7.2	8.2	7.2	7.5	8.4	7.0	-	-
Blood glucose (mg/dL)	-	193	-	297	-	-	-	-

Case Summaries [Injectable dosage form]

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 50s	Mitral valve replacement, tricuspid valve repair, maze operation, operative haemorrhage, postoperative haemorrhage (smoking)	6 g for 1 day	**Convulsion** <Medical history> Chronic renal failure Day 1 of administration (day of completion): In the morning, the patient was transferred to an operating room. During the operation, 6 g of tranexamic acid was used. Six hours and thirty minutes later, the patient was moved to intensive care unit (ICU) (after the patient became conscious, propofol was administered for sedation). The patient was followed up while undergoing continuous hemodialysis-filtration (CHDF). 1 day after completion: In the morning, the patient was staring at one point and then presented with generalised tonic convulsion (resolved within 1 minute; before the onset of convulsion, the patient was able to communicate, with Glasgow coma scale [GCS] score [level of consciousness] of 15 points.) Ten minutes later, convulsion recurred, for which diazepam 5 mg was intravenously administered. Fifty five minutes later, generalised convulsion developed, for which diazepam 5 mg was intravenously administered. One hour later, neither head CT nor blood test showed any abnormalities. Two hours and thirty minutes later, generalised convulsion recurred, for which bolus intravenous injection of propofol 10 mg was given (the patient had been receiving propofol at a maintenance dose of 100 mg/hr). After consultation with a neurologist, the patient was followed up. Five hours later, the patient experienced generalised convulsion, which resolved with an intravenous injection of midazolam 6 mg. Administration of phenytoin was started. 2 days after completion: The patient recovered from generalised convulsion. 3 days after completion: The second head CT also showed no abnormality. 4 days after completion:

				Administration of midazolam was discontinued. 5 days after completion: Extubation was performed (without convulsion), with improvement in the level of consciousness. Administration of propofol was discontinued. 8 days after completion: The patient was moved to the general ward. 17 days after completion: Magnetic resonance imaging (MRI) did not show any source of the convulsion. 19 days after completion: Administration of phenytoin was discontinued. 41 days after completion: Symptoms improved, and the patient was discharged from the hospital.
	Concomitant medications: cefazolin sodium, carperitide (genetical recombination), nicardipine hydrochloride, dopamine hydrochloride, nitroglycerin, propofol			

Laboratory Examination

	Day 1 of administration		1 day after completion	2 days after completion	3 days after completion
WBC (/μL)	5,900	6,200	11,600	13,900	10,800
RBC ($\times 10^4$/μL)	305	368	359	357	342
Hemoglobin (g/dL)	9.1	11.1	11.1	10.9	10.5
Hematocrit (%)	27.2	34.1	33.2	33.7	32.4
PLT ($\times 10^4$/μL)	18.8	18.0	18.2	16.0	11.7
Blood glucose (mg/dL)	148	150	158	149	117
BUN (mg/dL)	12	16	18	22	30
Blood creatinine (mg/dL)	4.2	4.4	4.2	4.4	4.3
Serum sodium (mEq/L)	135	137	138	136	136
Serum potassium (mEq/L)	3.7	3.9	4.0	4.3	4.0
Serum chloride (mg/dL)	104	105	104	101	101

3 Iguratimod

Brand Name (name of company)	Careram Tablet 25 mg (Eisai Co., Ltd.), KOLBET Tablet 25 mg (Toyama Chemical Co., Ltd.)
Therapeutic Category	Miscellaneous metabolism agents-Miscellaneous
Indications	Rheumatoid arthritis

PRECAUTIONS (underlined parts are revised)

Contraindications

Patients on treatment with warfarin

Interaction (contraindications for concomitant use)

Warfarin [Clinical symptoms and measures to be taken: Serious haemorrhage due to increased effect of warfarin after concomitant use of iguratimod with warfarin have been reported. When patients are required to receive warfarin therapy, warfarin should be administered preferentially and this drug should not be administered. Mechanism and risk factors: The mechanism is unknown.]

Reference Information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) for the past 8 months (from initial marketing to May 17, 2013)

- Haemorrhage or abnormalities on tests of hemostasis (increased PT-INR)

associated with possible interaction between iguratimod and warfarin: 6 cases (1 fatal case)

The number of patients using this drug estimated by MAHs: 2,879 (from initial marketing to May 2013)

Launched in Japan: September 2012

Case Summary

See a case summary (p.6) in "1. Severe Haemorrhages Associated with Suspected Interaction between Antirheumatic Iguratimod and Warfarin" of this issue of PMDSI.

4

Revision of Precautions (No. 246)

(1) Drugs

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated April 23 and May 17, 2013 (excluding those presented in "3. Important Safety Information" of this Bulletin).

1 Diuretics

Tolvaptan

Brand Name	Samsca tablets 7.5 mg, 15 mg (Otsuka Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction**: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), γ-GTP, Al-P, bilirubin, etc. may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued immediately and appropriate measures should be taken.

2 Respiratory organ agents-Bronchodilators

Tiotropium Bromide Hydrate

Brand Name	Spiriva Inhalation Capsules 18 μg, Spiriva 2.5 μg Respimat 60 puffs (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Anaphylaxis**: Anaphylaxis (urticaria, angioedema, dyspnoea, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

3 Peptic ulcer agents

Esomeprazole Magnesium Hydrate

Brand Name	Nexium Capsules 10 mg, 20 mg (AstraZeneca K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Interstitial pneumonia**: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray and chest CT scan should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

4 Anticoagulants

Dabigatran Etexilate Methanesulfonate

Brand Name	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Precautions of Indications	This drug should not be used as anticoagulant therapy after heart valve prosthesis implantation.

Other Precautions

In an overseas Phase II comparative, range-finding study of this drug and warfarin involving a total of 252 patients undergoing artificial heart valve replacement (within 3 to 7 days or at least 3 months after operation), which is off-label use of this drug, thromboembolic and haemorrhagic events occurred more frequently in patients receiving this drug than those receiving warfarin. In particular, haemorrhagic pericardial effusion occurred in patients who started receiving this drug within 3 to 7 days after an operation.

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5 Antineoplastics-Miscellaneous

Nilotinib Hydrochloride Hydrate

Brand Name

Tasigna Capsules 150 mg, 200 mg (Novartis Pharma K.K.)

Important Precautions

Hyperglycaemia may occur. Blood glucose levels should be measured periodically during administration of this drug, and if any abnormalities are observed, appropriate measures should be taken.

Adverse Reactions (clinically significant adverse reactions)

Hyperglycaemia: Hyperglycaemia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures should be taken.

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6 Acting mainly on gram-positive and gram-negative bacteria

Amoxicillin Hydrate

Brand Name

Sawacillin Capsules 125, 250, Sawacillin Fine Granules 10%, Sawacillin Tablets 250 (Astellas Pharma Inc.), PASETOCIN Capsule 125, 250, PASETOCIN Fine Granules 10%, PASETOCIN Tablets 250 (Kyowa Hakko Kirin Co., Ltd.) and the others

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, headache, arthralgia, erythaema and blister of the skin and mucous membranes, pustule, tension, burning sensation and pain of skin are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Interstitial pneumonia, eosinophilic pneumonia: Interstitial pneumonia or eosinophilic pneumonia may occur. If cough, dyspnoea, pyrexia, etc. are observed, examinations including chest X-ray and chest CT scan should be performed immediately. If interstitial pneumonia or eosinophilic pneumonia is suspected, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

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7 Acting mainly on gram-positive and gram-negative bacteria

Potassium Clavulanate/Amoxicillin Hydrate

Brand Name

Augmentin Combination Tablets 125SS, 250RS, CLAVAMOX combination Dry Syrup for pediatric use (GlaxoSmithKline K.K.)

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme may occur. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Interstitial pneumonia, eosinophilic pneumonia: Interstitial pneumonia or eosinophilic pneumonia may occur. If cough, dyspnoea, pyrexia, etc. are observed, examinations including chest X-ray and chest CT scan should be performed immediately. If interstitial pneumonia or eosinophilic pneumonia is suspected, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

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8 Acting mainly on gram-positive bacteria and mycoplasma

Clarithromycin

Brand Name

Clarith tab. 200, Clarith tab. 50 for pediatric, Clarith dry syrup 10% for pediatric (Taisho Pharmaceutical Co., Ltd.), KLARICID TABLET 200 mg, KLARICID TABLET 50 mg FOR PEDIATRIC USE, KLARICID DRY SYRUP 10% FOR PEDIATRIC USE (Abbott Japan Co., Ltd.), and the others

Adverse Reactions (clinically significant adverse reactions)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

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9 Antibiotics-Miscellaneous

Lansoprazole/Amoxicillin Hydrate/Clarithromycin

Brand Name

LANSAP 400, 800 (Takeda Pharmaceutical Company Limited)

Adverse Reactions (clinically significant adverse reactions)

(Amoxicillin Hydrate)
Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, headache, arthralgia, erythaema and blister of the skin and mucous membranes, pustule, tension, burning sensation and pain of skin are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Interstitial pneumonia, eosinophilic pneumonia**: Interstitial pneumonia or eosinophilic pneumonia may occur. If cough, dyspnoea, pyrexia, etc. are observed, examinations including chest X-ray and chest CT scan should be performed immediately. If interstitial pneumonia or eosinophilic pneumonia is suspected, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

(Clarithromycin)
Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme: Toxic epidermal necrolysis, oculomucocutaneous syndrome or erythema multiforme may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

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10 Antibiotics-Miscellaneous

Lansoprazole/Amoxicillin Hydrate/Metronidazole

Brand Name

LAMPION Pack (Takeda Pharmaceutical Company Limited)

Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, acute generalised exanthematous pustulosis**: Toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, headache, arthralgia, erythaema and blister of the skin and mucous membranes, pustule, tension, burning sensation and pain of skin are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Interstitial pneumonia, eosinophilic pneumonia**: Interstitial pneumonia or eosinophilic pneumonia may occur. If cough, dyspnoea, pyrexia, etc. are observed, examinations including chest X-ray and chest CT scan should be performed immediately. If interstitial pneumonia or eosinophilic pneumonia is suspected, administration of this drug should be discontinued and appropriate measures including administration of corticosteroids should be taken.

11 **Chemotherapeutics-Miscellaneous**

Terbinafine Hydrochloride (oral dosage form)

Brand Name	Lamisil Tablets 125 mg (Novartis Pharma K.K.) and the others
Important Precautions	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis or erythroderma (exfoliative dermatitis) may occur. During administration of this drug, patients should be carefully monitored.
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, erythroderma (exfoliative dermatitis):** Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalised exanthematous pustulosis or erythroderma (exfoliative dermatitis) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. **Drug-induced hypersensitivity syndrome**: Rash and pyrexia may occur as the initial symptoms followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, swollen lymph nodes, increased white blood cells, eosinophilia, and atypical lymphocytes. Patients should be carefully monitored, and if such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken. The reactivation of viruses including Human Herpes virus 6 (HHV-6) has been found to be frequently associated with drug-induced hypersensitivity syndrome. Symptoms such as rash, pyrexia, and hepatic dysfunction may relapse or be prolonged even after discontinuing administration, and thus caution should be exercised. **Subacute cutaneous lupus erythematosus**: Subacute cutaneous lupus erythematosus may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

12 **Over-the-counter**

Preparations Containing Tranexamic Acid (mainly containing vitamins)

Brand Name	TRANSINO (Daito Pharmaceutical Co., Ltd.)
When not to use the product	This product should not be used in the following persons: Persons undergoing dialysis (Convulsions may occur).

13 **Anticoagulants**

Warfarin Potassium

Brand Name	Warfarin Tablets 0.5 mg, 1 mg, 5 mg, Warfarin Granules 0.2% (Eisai Co., Ltd.) and the others
Contraindications	Patients on treatment with iguratimod
Interaction (contraindications for concomitant use)	Iguratimod [Clinical symptoms and measures to be taken: Iguratimod may increase the effects of this drug. When patients are required to receive this drug, treatment with this drug should be performed preferentially and iguratimod should not be administered. Mechanism and risk factors: The mechanism is unknown.]

(2) Medical Devices

This section presents details of revisions to the Precautions section of package inserts and brand names of medical devices that have been revised in accordance with the Notification dated May 20, 2013.

1 Magnetic Resonance Imaging System

Contraindications

(1) Regarding medical devices, etc. that are implanted or placed in the body
In general, MRIs should not be performed in patients with implantation or placement of medical devices, etc. containing metal. [Migration, failure, breakage, malfunction, or burn of implanted or placed medical devices may occur in a patient's body.]
Exceptions are medical devices that have been conditionally demonstrated to be compatible with MRI systems. Before performing MRI, imagining conditions, etc. should be confirmed by referring to the package insert, etc. of the medical device in a patient's body.

(2) Regarding medical devices, etc. that are expected to be brought to the MRI room
Any medical devices, etc. containing metal should not be brought to the MRI room. [These devices may be magnetically attracted to an MRI system, broken or damaged, or cause burns, etc.]
Exceptions are medical devices that have been conditionally demonstrated to be compatible with MRI systems. Before performing an MRI, compatible magnetic field strength should be confirmed by referring to the package insert, etc. of the medical device to be used.

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 new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of new drugs. It is imposed that its Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for 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 adverse drug reactions. EPPV is specified as a condition of approval.

(As of June 1, 2013)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Levetiracetam E Keppra Tablets 250 mg, 500 mg*1	UCB Japan Co. Ltd	May 31, 2013
Istradefylline NOURIAST Tablets 20 mg	Kyowa Hakko Kirin Co., Ltd.	May 30, 2013
Rufinamide Inovelon Tablets 100 mg, 200 mg	Eisai Co., Ltd.	May 29, 2013
Acamprosate Calcium Regtect Tablets 333 mg	Nippon Shinyaku Co., Ltd.	May 27, 2013
Ofatumumab (Genetical Recombination) Arzerra for I.V. infusion 100 mg, 1000 mg	Glaxo SmithKline K.K.	May 24, 2013
Tocilizumab (Genetical Recombination) ACTEMRA 162 mg Syringe for SC Injection, ACTEMRA 162 mg Auto-Injector for SC Injection	Chugai Pharmaceutical Co., Ltd.	May 24, 2013
Exenatide BYDUREON for Subcutaneous Injection 2 mg	Astra Zeneca K.K.	May 16, 2013
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Stribild Combination Tab.	Japan Tobacco Inc.	May 14, 2013
Paromomycin Sulfate AMEPAROMO capsules 250 mg	Pfizer Japan Inc.	April 12, 2013
Botulinum Toxin Type B NerBloc for Intramuscular Injection 2500 Units	Eisai Co., Ltd.	March 27, 2013
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 60 μg*2	Ferring Pharmaceuticals Co., Ltd.	March 25, 2013
Regorafenib Hydrate Stivarga tablets 40 mg	Bayer Yakuhin, Ltd.	March 25, 2013
Methadone Hydrochloride METHAPAIN Tablets 5 mg, 10 mg	Teikoku Seiyaku Co., Ltd.	March 25, 2013
Fesoterodine Fumarate Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	March 15, 2013

Certolizumab Pegol (Genetical Recombination) Cimzia 200 mg Syringe for S.C. Injection	UCB Japan Co. Ltd	March 8, 2013
Insulin Degludec (Genetical Recombination) TRESIBA Injection FlexTouch, TRESIBA Injection Penfill	Novo Nordisk Pharma Ltd.	March 7, 2013
Monobasic sodium phosphate monohydrate/Dibasic sodium phosphate anhydrous Phosribbon Combination Granules*3	Zeria Pharmaceutical Co., Ltd.	March 4, 2013
Fexofenadine Hydrochloride/Pseudoephedrine Hydrochloride dellegra Combination Tablets	Sanofi K.K.	February 28, 2013
Sodium Risedronate Hydrate BENET Tablets 75 mg.	Takeda Pharmaceutical Company Limited	February 28, 2013
Sodium Risedronate Hydrate Actonel Tab. 75 mg	Ajinomoto Pharmaceuticals Co., Ltd.	February 28, 2013
Rotigotine Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013
Levocarnitine L-Cartin FF oral solution 10%, L-Cartin FF injection 1000 mg	Otsuka Pharmaceutical Co., Ltd.	February 26, 2013
Apixaban Eliquis tablets 2.5 mg, 5 mg	Bristol-Myers K.K.	February 26, 2013
Atovaquone/Proguanil Hydrochloride Malarone Combination Tablets	GlaxoSmithKline K.K.	February 22, 2013
Tetrabenazine CHOREAZINE Tablets 12.5 mg	Alfresa Pharma Corporation	February 22, 2013
Famciclovir Famvir Tab. 250 mg*4	Asahi Kasei Pharma Corporation	February 21, 2013
Sodium Phenylbutyrate Buphenyl Tablets 500 mg, Buphenyl Granules 94%	Orphan Pacific, Inc.	January 17, 2013
Lanreotide Acetate Somatuline 60 mg for s.c. Injection, Somatuline 90 mg for s.c. Injection, Somatuline 120 mg for s.c. Injection	Teijin Pharma Limited.	January 17, 2013
Omega-3-acid ethyl esters LOTRIGA Granular Capsule 2 g	Takeda Pharmaceutical Company Limited	January 10, 2013
Carmustine Gliadel 7.7 mg Implant	Nobelpharma Co., Ltd.	January 9, 2013
Tobramycin TOBI Inhalation solution 300 mg	Novartis Pharma K.K.	January 9, 2013
Desmopressin Acetate Hydrate MINIRINMELT OD Tablet 120 μg, 240 μg*5	Ferring Pharmaceuticals Co., Ltd.	December 21, 2012
Irbesartan/Amlodipine Besilate AIMIX Combination Tablet LD, HD	Dainippon Sumitomo Pharma Co., Ltd.	December 19, 2012
Olanzapine Zyprexa Rapid Acting Intra-Muscular Injection 10 mg	Eli Lilly Japan K.K.	December 3, 2012

*1 An additional administration for “pediatrics”

*2 An additional indication for “treatment of patients with central diabetes insipidus”

*3 An additional indication for “treatment of patients with hypophosphataemia”

*4 An additional indication for “treatment of patients with herpes simplex”

*5 An additional indication for “treatment of patients with central diabetes insipidus”