Pharmaceuticals and Medical Devices Safety Information

No. 316 September 2014

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare (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 (http://www.mhlw.go.jp/, only available in Japanese language).

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Pharmaceuticals and Medical Devices Safety Information

No. 316 September 2014

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

[Outline of Information]

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1	**Project of Japan Drug Information Institute in Pregnancy**		The MHLW established the Japan Drug Information Institute in Pregnancy (JDIIP) in the National Center for Child Health and Development in October 2005 to provide consultation services and perform surveys. The system for consultation services and prompt information collection of the JDIIP was strengthened in FY 2014 by receiving the cooperation of newly joined hospitals. Details are presented in this section.	4
2	**Effects of Angiotensin II Receptor Blockers and Angiotensin Converting Enzyme Inhibitors on Pregnant Women and Foetuses**	*C*	Angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors are contraindicated in pregnant women; however, cases have been reported in patients who were continuously treated with ARBs or ACE inhibitors even after pregnancy was diagnosed. Adverse events possibly associated with maternal ARB or ACE inhibitor use have also been reported in foetuses. The PMDA, therefore, issued *PMDA Alert for Proper Use of Drugs* to fully inform healthcare professionals about the proper use of ABRs and ACE inhibitors. Details are presented in this section.	10
3	**Revision of Precautions (No. 259)**		Pramipexole hydrochloride hydrate (and 9 others)	18
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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

ACE	Angiotensin-converting enzyme
ADR	Adverse drug reaction
AFI	Amniotic Fluid Index
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
ARB	Angiotensin II receptor blocker
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
EPPV	Early Post-marketing Phase Vigilance
FHR	Foetal heart rate
JDIIP	Japan Drug Information Institute in Pregnancy
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
TEN	Toxic Epidermal Necrolysis
γ-GTP	gamma-glutamyl transpeptidase

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Project of Japan Drug Information Institute in Pregnancy

1. Introduction

The MHLW established the JDIIP at the National Center for Child Health and Development in October 2005 to provide a variety of drug consultation services to pregnant women and women who wish to become pregnant based on the latest scientific evidence. The JDIIP also evaluates pregnancy outcome in consultation clients to establish new evidence. The activities of the JDIIP have been introduced in PMDSI No. 268, 279, and 305.

[References]

- JDIIP website
  http://www.ncchd.go.jp/kusuri/index.html
- PMDSI No.268
  http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-268.pdf
- PMDSI No.279
  http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-279.pdf
- PMDSI No.305
  http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-305.pdf

2. The consultation services and analyses performed by the Japan Drug Information Institute in Pregnancy

The JDIIP receives over 1 000 consultations annually. The number of consultations received by the institute suggests that possible adverse effects of drugs used during pregnancy on foetuses are widely known. Congenital anomalies, such as external malformation, are of the utmost concern to consultation clients, and long-term effects on child development have also been reported recently. Thorough evaluation of information and risks of such long-term effects is also essential.

Evaluation of information collected so far revealed that even healthcare professionals, as well as consultation clients, do not adequately understand the risks in some cases. Namely, risks associated with the use of ACE inhibitors and ARBs are often misunderstood (see page 10). The ACE inhibitors and ARBs should be switched to other types of drugs during pregnancy; however, some consultation clients are not aware of the need to switch the medication. On the other hand, some consultation clients overestimate the risks and discontinue the necessary treatment, resulting in difficulty to maintain the maternal health. It may lead to adverse effects on pregnancy and delivery.

It is important to weigh potential risks against potential benefits of using drugs during pregnancy. For example, use of sodium valproate during pregnancy may increase the incidence of congenital anomaly and adversely affect children's intelligence quotient. However, the benefits including prevention of epileptic seizures are crucial, and sodium valproate could be used during pregnancy if other medications fail to control epilepsy. For prophylaxis of migraine, drugs other than sodium valproate are recommended during pregnancy. Sodium valproate for prophylaxis of migraine is contraindicated during pregnancy in the United States. Whether to use a particular drug should be decided based on the purpose of use as well as the potential risks.

Information on how drugs affect pregnancy is gradually being clarified. Risk assessment will be changed based on the collected information. Drug benefits will also be changed depending on the availability of alternative drugs and other therapies. Whether to use a particular drug should therefore be decided based on the latest information.

3. Increase of cooperating institutions

The system for consultation services and prompt information collection of the JDIIP was strengthened in fiscal year 2014, by receiving the cooperation of 4 hospitals (Fukushima Medical University Hospital, Hamamatsu University Hospital, Mie University Hospital, and University of Miyazaki Hospital) newly joined, in order to enhance the accessibility. The cooperating institutions are introduced below.

Healthcare professionals are encouraged to introduce the consultation services of JDIIP to pregnant women or other people who are concerned about the effects of drugs they have used. See our website for the referral procedure.

Consultation services and procedure
http://www.ncchd.go.jp/kusuri/process/index.html (only available in Japanese language)

	Name of medical institution	Contact information, reception hours, etc.
1	Japan Drug Information Institute in Pregnancy	2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 in National Center for Child Health and Development TEL: (+81)-3-5494-7845 Reception hours: 10:00 –12:00, 13:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.ncchd.go.jp/kusuri/index.html
Cooperating hospitals (◎: Joined since 2014)		
2	Hokkaido University Hospital	Kita 14, Nishi 5, Kita-ku, Sapporo-city, Hokkaido 060-8648 TEL: (+81)-11-706-3455 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-11-706-7616 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)
3	Iwate Medical University Hospital	19-1 Uchimaru, Morioka-city, Iwate 020-8505 TEL: (+81)-19-624-5263 (Pregnancy and drugs counseling desk: Direct call) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
4	Tohoku University Hospital	1-1 Seiryo-machi, Aoba-ku, Sendai-city, Miyagi 980-8574 TEL: (+81)-22-717-7000 (Hospital’s main switchboard number) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.hosp.tohoku.ac.jp/
5 ◎	Fukushima Medical University Hospital	1 Hikarigaoka, Fukushima-city, Fukushima 960-1295 TEL: (+81)-24-547-1226 Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) HP ： http://www.fmu.ac.jp/

6	Maebashi Red Cross Hospital	3-21-36 Asahi-cho, Maebashi-city, Gunma 371-0014 TEL: (+81)-27-224-4585 (Division of Pharmacy: Extension 7709) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.maebashi.jrc.or.jp/
7	Tsukuba University Hospital	2-1-1 Amakubo, Tsukuba-city, Ibaraki 305-8576 TEL: (+81)-29-896-7171 FAX: (+81)-29-896-7170 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
8	Chiba University Hospital	1-8-1 Inohana, Chuo-ku, Chiba-city, Chiba 260-8677 TEL: (+81)-43-226-2628 (Drug Information, Division of Pharmacy) Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
9	Saitama Medical University Hospital	38 Morohongo Moroyama-machi, Iruma-gun, Saitama 350-0495 TEL: (+81)-49-276-1297 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 15:00 – 17:00 (Monday to Saturday, excluding national holidays)
10	Toranomon Hospital	2-2-2 Toranomon, Minato-ku, Tokyo 105-8470 TEL: (+81)-3-3588-1111 (Extension 3410) FAX: (+81)-3-3505-1764 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
11	St. Luke’s International Hospital	9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560 TEL: (+81)-3-5550-2412 FAX: (+81)-3-5550-2563 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
12	Yokohama City University Hospital	3-9 Fukuura, Kanazawa-ku, Yokohama-city, Kanagawa 236-0004 TEL: (+81)-45-787-2800 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.fukuhp.yokohama-cu.ac.jp/
13 ◎	Hamamatsu University Hospital	1-20-1 Handayama, Higashi-ku, Hamamatsu-city, Shizuoka 431-3192 TEL: (+81)-53-435-2637 (Regional Cooperation Unit) FAX: (+81)-53-435-2849 Reception hours: 8:30 – 18:00 (Monday to Friday, excluding national holidays and year-end/new-year) URL: http://www.hama-med.ac.jp/hos_index.html

14	Shinshu University Hospital	3-1-1 Asahi, Matsumoto-city, Nagano 390-8621 TEL: (+81)-263-37-3022 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-263-37-3072 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
15	Niigata University Medical & Dental Hospital	1-754 Asahimachi-dori, Chuo-ku, Niigata-city, Niigata 951-8520 TEL: (+81)-25-227-2895 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-25-227-2791 Reception hours: 13:30 – 16:00 (Monday to Friday, excluding national holidays)
16	National Hospital Organization Kanazawa Medical Center	1-1 Shimoishibiki-machi,Kanazawa-city, Ishikawa 920-8650 TEL: (+81)-76-262-4161 Reception hours: 9:00 – 16:30 (Monday to Friday, excluding national holidays) URL: http://www.kanazawa-hosp.jp/pv/preg.htm
17	National Hospital Organization Nagara Medical Center	1300-7 Nagara, Gifu-city, Gifu 502-8558 TEL: (+81)-58-232-7755 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-58-295-0077 Reception hours: 10:00 – 16:00 (Monday to Friday, excluding national holidays)
18	Japanese Red Cross Nagoya Daiichi Hospital	3-35 Michishita-cho, Nakamura-ku, Nagoya-city, Aichi 453-8511 TEL: (+81)-52-481-5111 (Division of Pharmacy: Extension 38167) FAX: (+81)-52-482-7733 Reception hours: 13:00 – 16:00 (Monday to Friday, excluding national holidays)
19 ◎	Mie University Hospital	2-174, Edobashi Tsu-city, Mie 514-8507 TEL: (+81)-59-231-5552 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 8:30 – 16:00 (Monday to Friday, excluding national holidays)
20	University Hospital, Kyoto Prefectural University of Medicine	465 Kajii-cho, Hirokoji agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto-City, Kyoto 602-8566 TEL: (+81)-75-251-5862 (Drug Information, Division of Pharmacy) FAX: (+81)-75-251-5859 (same as above): Reception hours: 9:00 – 17:00 (Monday to Friday, excluding national holidays)

21	Osaka Medical Center and Research Institute for Maternal and Child Health	840 Murodo-cho, Izumi-city, Osaka 594-1101 TEL: (+81)-725-56-5537 (Outpatient department for pregnancy and drugs) Reception hours: 10:00 – 12:00, 14:00 – 17:00 (Monday to Friday, excluding national holidays) URL: http://www.mch.pref.osaka.jp/hospital/department/pharmacy/pharmacy03.html
22	Nara Medical University Hospital	840 Shijo-cho, Kashihara-city, Nara 634-8522 TEL: (+81)-744-22-3051 (Division of Pharmacy: Extension 3565) FAX: (+81)-744-29-8027 Reception hours: 8:30 – 16:00 (Monday to Friday, excluding national holidays) URL: http://www.naramed-u.ac.jp/~gyne/kusuri.html
23	Kobe University Hospital	7-5-2 Kusunoki-cho, Chuo-ku, Kobe-city, Hyogo 650-0017 TEL: (+81)-78-382-5111 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours:13:00 – 17:00 (Monday to Friday, excluding national holidays)
24	National Hospital Organization Okayama Medical Center	1711-1 Tamasu, Kita-ku, Okayama-city, Okayama 701-1192 TEL: (+81)-86-294-9556 (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-86-294-9557 Reception hours: 8:30 – 18:00 (Monday to Friday, excluding national holidays) URL: http://okayamamc.jp/04_bumon/04-04_bumon/04-04_03-02yakuzai.html
25	Hiroshima University Hospital	1-2-3 Kasumi, Minami-ku, Hiroshima-city, Hiroshima 734-8551 TEL: (+81)-82-257-5079 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)
26	National Hospital Organization Shikoku Medical Center for Children and Adults	2-1-1 Senyu-cho, Zentsuji-city, Kagawa 765-8507 TEL: (+81)-877-62-1000 FAX: (+81)-877-62-6311 Reception hours: 8:30 – 17:00 (Monday to Friday, excluding national holidays)
27	Tokushima University Hospital	2-50-1 Kuramoto-cho, Tokushima-city, Tokushima 770-8503 TEL: (+81)-70-6586-0831 Reception hours: 9:00 – 16:00 (Monday to Friday, excluding national holidays)

28 ◎	University of Miyazaki Hospital	5200 Kihara, Kiyotake-cho, Miyazaki-city, Miyazaki 889-1692 TEL: (+81)-985-85-1512 (Please ask for “Outpatient service for pregnancy and drugs”) Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays) URL: http://www.med.miyazaki-u.ac.jp/home/hospital/outpatient/5008/
29	Kyushu University Hospital	3-1-1 Maidashi, Higashi-ku, Fukuoka-city, Fukuoka 812-8582 TEL: (+81)-92-642-5900 Reception hours: 14:00 – 17:00 (Monday to Friday, excluding national holidays)
30	Kagoshima City Hospital	20-17 Kajiya-cho, Kagoshima-city, Kagoshima 892-8580 TEL: (+81)-99-224-2101 (Pharmacy department: Extension 2603) (Please ask for “Outpatient service for pregnancy and drugs”) FAX: (+81)-99-224-9916 Reception hours: 8:30 – 17:15 (Monday to Friday, excluding national holidays)
31	Okinawa Chubu Hospital	281 Miyazato, Uruma-city, Okinawa 904-2293 TEL: (+81)-98-973-4111 (Please ask for “Outpatient service for pregnancy/breastfeeding and drugs”) Reception hours: 13:00 – 16:00 (Tuesday, Thursday, and Friday, excluding national holidays)

2

Effects of Angiotensin II Receptor Blockers and Angiotensin Converting Enzyme Inhibitors on Pregnant Women and Foetuses

Antihypertensive treatment with ARBs and ACE inhibitors are known to adversely affect the foetus and are contraindicated during pregnancy. Although cautions have been issued in the alert for proper use of drug prepared and distributed by the marketing authorization holder (MAHs) in 2008, cases of continuous use of ARBs or ACE inhibitors during pregnancy and possible adverse effects on foetuses are continuously reported in Japan.

To ensure proper use of ARBs and ACE inhibitors in pregnant women or women who may be pregnant, the PMDA posted "*PMDA Alert for Proper Use of Drugs*"* on its website (http://www.pmda.go.jp/english/service/pdf/request/No10.pdf). The MAHs of ARBs and ACE inhibitors are also providing information to healthcare professionals by using the material.

Please check the PMDA's website for "*PMDA Alert for Proper Use of Drugs*." Your cooperation to thoroughly ensure proper use of ARBs and ACE inhibitors would be appreciated.

* See the PMDA's Medical Product Information web page for details of "*PMDA Alert for Proper Use of Drugs*" and past information materials.
http://www.pmda.go.jp/english/service/request.html

Reference (mechanism of action)
Adverse effects of ACE inhibitors and ARBs in pregnancy. (*Adverse drug reaction (ADR) bulletin*, No.246, p943-946, 2007)

PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No.10 September 2014

Adverse Events in Pregnant Women and Foetuses Associated with Use of Angiotensin II Receptor Blockers and Angiotensin Converting Enzyme Inhibitors

ARBs or ACE inhibitors are drugs that should not be administered to pregnant women because adverse foetal events have been reported. In Japan, several cases have been intermittently reported in patients who were continuously treated with ARBs or ACE inhibitors even after pregnancy was diagnosed. Adverse events possibly associated with maternal ARB or ACE inhibitor use have also been reported intermittently in foetuses.

Healthcare professionals are encouraged to review the following precautions. Please pay careful attention when administering ARBs or ACE inhibitors.

- **ARBs and ACE inhibitors should not be administered to pregnant women or to women who may be pregnant.**
- **If pregnancy is confirmed during administration, this drug should be discontinued immediately.**
- **When women with child-bearing potential need to be treated with ARBs or ACE inhibitors, they should be informed that ARBs or ACE inhibitors can affect a foetus and advised repeatedly that they should consult with their physician immediately if pregnancy is confirmed.**

■ Please note the precautions in the package inserts.

Sample information on the Precautions in the package inserts of ARBs or ACE inhibitors is as follows:

Contraindications (This drug should not be administered to the following patients:)
Pregnant women or women who may be pregnant (See Use in Pregnant, Parturient and Nursing Women section)

Use in Pregnant, Parturient, and Nursing Women
This drug should not be administrated to pregnant women or to women who may be pregnant. If pregnancy is diagnosed during administration, this drug should be discontinued immediately.
(Foetal or neonatal death, oligohydramnios, foetal or neonatal hypotension, renal failure, hyperkalaemia, skull hypoplasia, and extremity contracture/malformation of brain, skull, or face/pulmonary dysplasia possibly caused by oligohydramnios, etc. have been reported in pregnant patients in their second or third trimester treated with ARBs including this drug or ACE inhibitors. An overseas retrospective epidemiological study suggested that the relative risk of foetal malformation during the first trimester was higher in the group of ACE inhibitor users than the group of antihypertensive drug nonusers.)

See the package inserts for other precautions on ARBs and ACE inhibitors. Package inserts can be searched for and viewed on the PMDA website (http://www.pmda.go.jp) (only available in Japanese language).

Typical case reports

Case 1: Suspected drug-valsartan/amlodipine besilate

<table>
<tr><td rowspan="2">Sex/Age</td><td rowspan="2">Reason for use (complications)</td><td rowspan="2">Daily dose/ Treatment duration</td><td colspan="2">Adverse reactions</td></tr>
<tr><td colspan="2">Clinical course and therapeutic measures</td></tr>
<tr><td rowspan="5">Mother in her 30s

Male offspring</td><td rowspan="5">Hypertension (obesity)</td><td rowspan="5">valsartan 80 mg / amlodipine 5 mg (unknown)</td><td colspan="2">Mother; oligohydramnios, preterm premature rupture of membranes, and premature labour
Offspring; premature baby, hypocalvaria, renal tubular disorder, and low birth weight baby</td></tr>
<tr><td>Day 1 of administration (unknown gestation)</td><td>The mother started to take valsartan/amlodipine besilate. (gravida 1, para 1, smoker, no alcohol consumption, unknown if contraceptive was used)</td></tr>
<tr><td>Day of discontinuation (estimated 24-week gestation)</td><td>The mother visited her previous doctor because a pregnancy test was positive. The foetus appeared at 24 weeks gestation. The mother had anhydramnios. Administration of valsartan/amlodipine was discontinued.</td></tr>
<tr><td>1 day after discontinuation</td><td>The mother was referred to this hospital.</td></tr>
</table>

Sex/Age	Reason for use (complications)	Daily dose/ Treatment duration	Adverse reactions	
			Clinical course and therapeutic measures	
			8 days after discontinuation (estimated 25 weeks gestation)	The foetal bladder was identified. But there was no amniotic fluid.
			29 days after discontinuation (estimated 28 weeks gestation)	Amniotic fluid volume increased to a normal level.
			52 days after discontinuation (31 weeks gestation)	Membrane rupture and labour pain occurred. Emergency caesarean section was performed because the mother had given birth through caesarean section in the previous delivery. Findings of offspring: Sex, male Body height, 40.5 cm Body weight, 1 700 g 1-minute Apgar score, 6; 5-minute Apgar score, 9 Congenital anomaly, skull hypoplasia and renal tubular disorder Abnormality other than congenital anomaly, jaundice No pulmonary displasia
			108 days after discontinuation (56 days old)	Neonatal outcome was alive.
Concomitant medications: none				

Case 2: Suspected drug - telmisartan/hydrochlorothiazide

Sex/Age	Reason for use (complications)	Daily dose/ Treatment duration	Adverse reactions	
			Clinical course and therapeutic measures	
Mother in her 40s Male offspring	Hypertension	telmisartan 40 mg / hydrochlorothiazide 12.5 mg (34 days)	Mother; premature labour, oligohydramnios, and foetal growth restriction Offspring; hypotension, oliguria, renal impairment, low birth weight baby, and renal tubular acidosis	
			Approximately 4 years before administration	Hypertension was diagnosed but left untreated.
			Approximately 8 months before administration	Urine protein was positive but left untreated.
				The mother did not recognize her pregnancy until the day of delivery.
			Day 1 of administration (estimated 25 weeks gestation)	Telmisartan/hydrochlorothiazide was prescribed to treat hypertension. The mother started to take telmisartan/hydrochlorothiazide without recognizing her pregnancy.
			Date unknown	Foetal growth became poor.

Sex/Age	Reason for use (complications)	Daily dose/ Treatment duration	Adverse reactions	
			Clinical course and therapeutic measures	
			Day of discontinuation (34 days after administration) (estimated 30 weeks gestation)	The mother visited hospital A for a detailed examination of renal disorder. Her pregnancy was confirmed at this visit, and she was transferred to hospital B on the same day. The day of last menstruation was unknown; however, it was estimated to be 7 months ago, and the gestational age appeared to be approximately 34 weeks. Because the estimated body weight of the foetus was 1500 g, the foetal growth was considered equivalent to 30 weeks gestation. Oligohydramnios was found. Systolic blood pressure was 190 to 200 mmHg. The amniotic cavity was very small, and severe variable deceleration was frequently found on a foetal monitor. Emergency caesarean section was therefore performed. Delivery time was 17:48 (premature labour). Findings of offspring: Sex, male Body height, 39.9 cm Body weight, 1 400 g (very low birth weight baby) Congenital anomaly and other abnormalities were found: hypotension (average blood pressure was at the 40 mmHg), anuria, and renal failure were prolonged.
			1 day after discontinuation (1 day old)	Administration of dopamine hydrochloride to the offspring was started at 2:35. After administration, the offspring remained unresponsive to catecholamine, and oliguria was found.
			2 days after discontinuation (2 days old)	Furosemide 1.5 mg was administered intravenously for the treatment of oliguria at 15:00, but the offspring did not recover. The blood pressure was controlled by adjusting the dose of dopamine hydrochloride according to the offspring's condition.
			5 days after discontinuation (5 days old)	Urine output gradually increased and the dose of dopamine hydrochloride was reduced.
			6 days after discontinuation (6 days old)	Oliguria was remitted.
			9 days after discontinuation (9 days old)	Dopamine hydrochloride 3 γ was administered to the offspring. Although urine output increased, severe renal failure remained with 7.01 mg/dL of serum creatinine and 12.5 mg/dL of uric acid.
			11 days after discontinuation (11 day old)	Hypotension was remitted in the offspring.
			Date unknown	Renal tubular acidosis occurred in the offspring.
			40 days after discontinuation (40 days old)	Although serum creatinine tended to decrease in the offspring, metabolic acidosis remained. Administration of sodium bicarbonate was started in the offspring.
			62 days after discontinuation (62 days old)	The offspring was discharged from hospital. The offspring was followed up for mild renal failure and renal tubular acidosis as an outpatient.
Concomitant medicines: amlodipine besilate, carbocisteine, and bakumondoto				

Case 3: Suspected drug - candesartan cilexetil

Sex/Age	Reason for use (complications)	Daily dose/ Treatment duration	Adverse reactions / Clinical course and therapeutic measures	
Mother in her 30s Female offspring	Essential hypertension	12 mg (unknown)	Mother; oligohydramnios Offspring; foetal renal failure and transient limb extension disorder	
			Day of administration (3 years ago)	The mother started to take candesartan cilexetil for the treatment of essential hypertension. The mother had been followed up for her pregnancy since the first trimester in a local obstetric clinic. Her pregnancy was diagnosed to be complicated with chronic hypertension and the mother continued to take candesartan cilexetil. Blood pressure remained under 140/90 mmHg.
			Day of discontinuation (30 weeks and 2 days gestation)	The mother was transferred to a facility with a perinatal medical center because oligohydramnios was found at regular check up for pregnancy. Before transferring, amniotic fluid volume was not measured. Blood pressure was 145/88 mmHg and protein urine was negative at the arrival of the facility. Rupture of membranes was considered to be ruled out based on findings from the examination. Amniotic Fluid Index (AFI) was 0 cm. Estimated body weight of the foetus was 1 363 g and considered normal for gestational age. No morphological abnormalities was found in bilateral kidneys; however, no urine accumulation was identified in the bladder even from several examinations. Although her thorax was not bell-shaped, thoracic circumference/abdominal circumference was 0.74, indicating mild pulmonary hypoplasia. No abnormal morphology was found in other organs. Her physician considered that oligohydramnios was caused by foetal renal failure, and replaced candesartan cilexetil with methyldopa.
			5 days after discontinuation (31 weeks gestation)	Urine accumulation was found in the bladder 5 days after discontinuation of candesartan cilexetil.
			9 days after discontinuation (31 weeks and 4 days gestation)	The amniotic fluid volume increased 9 days after discontinuation of candesartan cilexetil. AFI was 2.3 cm. After that, the amniotic fluid volume did not decrease and AFI was 3 to 6 cm. The baseline foetal heart rate (FHR) had an upper limit of normal (160 bpm), baseline variability was low, and no temporary tachycardia was found at all. A week after discontinuation, the baseline FHR decreased to 140 bmp, and temporary tachycardia was frequently found. The blood pressure was not increased in the mother after the treatment was replaced with methyldopa.
			42 days after discontinuation (36 weeks and 2 days gestation)	Labour was induced with oxytocin because of premature rupture of membranes. The mother delivered vaginally. Findings of offspring: Sex, female Body height, 40.5 cm Body weight, 2 416 g 1-minute Apgar score, 8; 5-minute Apgar score, 8 Umbilical cord arterial blood pH, 7.305 Congenital anomaly and other abnormalities were found: The offspring cried in a small sterilized area for delivery. No obvious respiratory disorder was found. The chest X-ray test did not show thoracic hypoplasia. No skull hypoplasia was found. Mild transient limb extension disorder was found. Urinary output was found after 6 hours after birth. Serum creatinine was within the normal range. Urine beta 2 microglobulin slightly increased. The ultrasound test showed no abnormal morphology but increased brightness in the kidneys.
Concomitant medicines; unknown				

- Fifty-eight adverse events in 25 pregnant women and foetuses that are possibly associated with the use of ARBs or ARB combination products in pregnant women (reported between fiscal year 2011 and 2013)

Pregnant women

Type of ADRs	Term of adverse reaction	Number of ADR cases
Pregnancy, puerperium, and perinatal conditions	Oligohydramnios	9
	Premature labour	2
	Foetal growth restriction	2
	Preterm premature rupture of membranes	1
	Threatened labour	1
	Pre-eclampsia	1
	Polyhydramnios	1
Surgical intervention	Uterine dilation and evacuation	1

Foetuses/ neonates

Type of ADRs	Term of adverse reaction	Number of ADR cases
Congenital, familial, and genetic disorders	Premature baby	4
	Foetal death	2
	Osteogenesis imperfecta	2
	Pulmonary hypoplasia	2
	Rib hypoplasia	2
	Potter's syndrome	2
	Low birth weight baby	2
	Congenital absence of cranial vault	1
	Hypocalvaria	1
	Cleft lip and palate	1
	Phalangeal hypoplasia	1
	Patent ductus arteriosus	1
	Foetal malformation	1
	Congenital cystic kidney disease	1
	Congenital anomaly	1
Renal and urinary disorders	Renal failure neonatal	4
	Renal impairment	2
	Renal failure	1
	Renal tubular disorder	1
	Renal tubular acidosis	1
	Oliguria	1
Respiratory disorders	Neonatal asphyxia	1
	Respiratory failure	1
Musculoskeletal disorders	Joint contracture	1
Cardiovascular disorders	Hypotension	1
Nervous system disorders	Epilepsy	1
Hearing disorders	Hearing impaired	1

- Five adverse events in 3 pregnant women and foetuses that are possibly associated with the use of ACE inhibitors in pregnant women (reported between fiscal year 2011 and 2013)

Pregnant women

Type of ADRs	Term of adverse reaction	Number of ADR cases
Pregnancy, puerperium, and perinatal conditions	Oligohydramnios	1

Pregnant women

Type of ADRs	Term of adverse reaction	Number of ADR cases
Congenital, familial, and genetic disorders	Renal aplasia	1
	Congenital cystic kidney disease	1
Renal and urinary disorders	Renal failure	1
	Kidney enlargement	1

ARBs and ACE inhibitors approved in Japan

	Nonproprietary Name	Brand Name
ARBs	azilsartan	Azilva
	irbesartan	Avapro, Irbetan
	olmesartan medoxomil	Olmetec
	candesartan cilexetil	Blopress and the others
	telmisartan	Micardis
	valsartan	Diovan and the others
	losartan potassium	Nu-lotan and the others
ARB combination products	azilsartan/ amlodipine besilate	Zacras
	irbesartan/ amlodipine besilate	Aimix
	irbesartan/trichlormethiazide	Irtra
	olmesartan medoxomil/azelnidipine	Rezaltas
	candesartan cilexetil/amlodipine besilate	Unisia
	candesartan cilexetil/ hydrochlorothiazide	Ecard
	telmisartan/ amlodipine besilate	Micamlo
	telmisartan/ hydrochlorothiazide	Micombi
	valsartan/ amlodipine besilate	Exforge
	valsartan/ cilnidipine	Atedio
	valsartan/ hydrochlorothiazide	Co-dio
	losartan potassium/ hydrochloro thiazide	Preminent and the others

	Nonproprietary Name	Brand Name
ACE inhibitors	alacepril	Cetapril and the others
	imidapril hydrochloride	Tanatril and the others
	enalapril maleate	Renivace and the others
	captopril	Captoril and the others
	quinapril hydrochloride	Conan
	cilazapril hydrate	Inhibace and the others
	temocapril hydrochloride	Acecol and the others
	delapril hydrochloride	Adecut
	trandolapril	Preran, Odric, and the others
	benazepril hydrochloride	Cibacen and the others
	perindopril erbumine	Coversyl and the others
	lisinopril hydrate	Zestril, Longes, and the others

The JDIIP provides consultation services to women who are concerned about the influence of drugs on foetuses. Patients who need more detailed information can be referred to the JDIIP.

Please find further information on the JDIIP in the National Center for Child Health and Development at the following website:
http://www.ncchd.go.jp/kusuri/index.html
(Japanese language only)

About this information

* "PMDA Alert for Proper Use of Drugs" communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among ADR/infection cases reported in accordance with the Pharmaceutical Affairs Law.
* We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future.
* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibilities on them, but is provided to promote the proper use of drugs.

Contact: Office of Safety II Email: safety.info@pmda.go.jp

3

Revision of Precautions (No. 259)

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 August 6, 2014.

1 Antiparkinsonian agents

Pramipexole Hydrochloride Hydrate

Brand Name	(1) BI•Sifrol Tablets 0.125 mg, 0.5 mg (Nippon Boehringer Ingelheim Co., Ltd.), and the others (2) Mirapex-LA Tablets 0.375 mg, 1.5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction:** Hepatic dysfunction with elevations of aspartate aminotransferase (AST or glutamate oxaloacetate transaminase [GOT]), alanine aminotransferase (ALT or glutamate pyruvate transaminase [GPT]), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), and/or total bilirubin 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.

2 Diuretics

Tolvaptan

Brand Name	Samsca Tablets 7.5 mg, 15 mg, 30 mg (Otsuka Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Pancytopenia or thrombocytopenia:** Pancytopenia or thrombocytopenia may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

3 Antihypertensives

Carvedilol

Brand Name	Artist Tablets 1.25 mg, 2.5 mg, 10 mg, 20 mg (Daiichi Sankyo Company, Limited), and the others
Adverse Reactions (clinically significant adverse reactions)	**Toxic epidermal necrolysis (TEN) and/or oculomucocutaneous syndrome (Stevens-Johnson syndrome):** TEN and/or oculomucocutaneous syndrome 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.

4 Digestive organ agents-Miscellaneous

Infliximab (Genetical Recombination)
Infliximab (Genetical Recombination) [Infliximab Biosimilar 1]

Brand Name	Remicade for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corporation)
Adverse Reactions (clinically significant adverse reactions)	**Rhabdomyolysis:** Rhabdomyolysis may occur. . Caution should be exercised for feelings of weakness, myalgia, increased creatine kinase (creatine phosphokinase), and/or, increased blood and urine myoglobin. If these symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

5 Antidotes

Sugammadex Sodium

Brand Name	Bridion Intravenous Injections 200 mg, 500 mg (MSD K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Ventricular fibrillation, ventricular tachycardia, cardiac arrest, and/or severe bradycardia:** Ventricular fibrillation, ventricular tachycardia, cardiac arrest, and/or severe bradycardia may occur within a few minutes after injection of this drug. Patients should be carefully monitored for haemodynamics. If any abnormalities are observed, appropriate measures should be taken. **Arteriospasm coronary:** Arteriospasm coronary may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be taken immediately.

6 Antineoplastics-Miscellaneous

Carboplatin

Brand Name	Paraplatin Injections 50 mg, 150 mg, 450 mg (Bristol-Myers K.K.), and the others
Adverse Reactions (clinically significant adverse reactions)	**Tumour lysis syndrome:** Tumour lysis syndrome may occur. Patients should be carefully monitored by checking serum electrolyte levels and renal function test, etc. If any abnormalities are observed, administration of this drug should be discontinued, appropriate measures (*e.g.* administration of physiological saline solution and/or hyperuricaemia therapeutic agents, and dialysis) should be taken, and patients should be carefully monitored until recovery from such symptoms.

7 Acting mainly on gram-positive bacteria, gram-negative bacteria, rickettsia, and chlamydia

Doxycycline Hydrochloride Hydrate

Brand Name	Vibramycin Tablets 50 mg, 100 mg (Pfizer Japan Inc.)
Adverse Reactions (clinically significant adverse reactions)	**Drug-induced hypersensitivity syndrome:** Rash and/or pyrexia may occur as initial symptoms followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, lymphadenopathy, increased white blood cells, increased eosinophils, and appearance of atypical lymphocytes. Patients should be carefully monitored. If these symptoms are observed, administration of this drug should be discontinued, and appropriate measures should be taken. Signs and symptoms such as rash, pyrexia, and/or hepatic dysfunction may relapse or be prolonged even after discontinuing administration. Therefore, caution should be exercised.

8

Antibiotics-Miscellaneous

(1) Rabeprazole Sodium/Amoxicillin Hydrate/Metronidazole
(2) Lansoprazole/Amoxicillin Hydrate/Metronidazole

Brand Name	(1) Rabefine Pack (Eisai Co., Ltd.) (2) Lampion Pack (Takeda Pharmaceutical Company Limited)
Adverse Reactions (clinically significant adverse reactions)	**Haemorrhagic colitis:** Haemorrhagic colitis may occur. If symptoms such as abdominal pain, bloody stool, and frequent diarrhoea are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

9

Synthetic antibacterials

Linezolid

Brand Name	Zyvox Tablets 600 mg, Zyvox Injections 600 mg (Pfizer Japan Inc.)
Important Precautions	Metabolic acidosis including lactic acidosis may occur. Patients should be adequately advised to visit their doctor immediately if nausea and/or vomiting repeatedly occur. If these symptoms are observed or if signs and symptoms such as unexplained acidosis and/or decreased blood bicarbonate are observed, appropriate measures such as discontinuation of administration should be taken.
Adverse Reactions (clinically significant adverse reactions)	**Metabolic acidosis:** Metabolic acidosis including lactic acidosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken. **Hepatic dysfunction:** Hepatic dysfunction with elevations of AST (GOT), ALT (GPT), LDH, alkaline phosphatase, and/or γ-GTP may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

10

Antiprotozoans

Metronidazole (oral dosage form)

Brand Name	Flagyl Oral Tablets 250 mg (Shionogi & Co., Ltd.) and the others
Adverse Reactions (clinically significant adverse reactions)	**Haemorrhagic colitis:** Haemorrhagic colitis may occur when metronidazole is used for treatment of *Helicobacter pylori* infection. If abdominal pain, bloody stool, and frequent diarrhoea are observed, administration of this drug should be discontinued immediately, and appropriate measures should be taken.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early post-marketing phase vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the ADRs from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADRs. EPPV is specified as a condition of approval.

(As of September 1, 2014)

◎: Products for which EPPV was initiated after August 2, 2014

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	rituximab (genetical recombination) Rituxan Injection 10 mg/mL*1	Zenyaku Kogyo Co., Ltd.	August 29, 2014
◎	phenothrin Sumithrin Lotion 5%	Kracie Pharma, Ltd.	August 22, 2014
◎	tapentadol hydrochloride Tapenta Tablets 25 mg, 50 mg, 100 mg	Janssen Pharmaceutical K.K.	August 18, 2014
	fentanyl citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg*2	Hisamitsu Pharmaceutical Co., Inc.	June 20, 2014
	sorafenib tosilate Nexavar Tablets 200 mg*3	Bayer Yakuhin, Ltd.	June 20, 2014
	pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein) Prevenar 13 Suspension Liquid for Injections*4	Pfizer Japan Inc.	June 20, 2014
	azilsartan/amlodipine besilate Zacras Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 18, 2014
	natalizumab (genetical recombination) Tysabri. for I.V. Infusions 300 mg	Biogen Idec Japan Ltd.	June 4, 2014
	prasugrel hydrochloride Efient Tablets 3.75 mg, 5 mg	Daiichi Sankyo Company, Limited	May 27, 2014
	betaine Cystadane	ReqMed Company, Ltd.	May 27, 2014
	trifluridine/tipiracil hydrochloride Lonsurf Combination Tablets T15, T20	Taiho Pharmaceutical Co., Ltd.	May 26, 2014
	denosumab (genetical recombination) Ranmark Subcutaneous Injections 120 mg*5	Daiichi Sankyo Company, Limited	May 23, 2014
	enzalutamide Xtandi Capsules 40 mg	Astellas Pharma Inc.	May 23, 2014
	valsartan/cilnidipine Atedio Combination Tablets	Ajinomoto Pharmaceuticals Co., Ltd	May 23, 2014

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
tofogliflozin hydrate (1) Deberza Tablets 20 mg (2) Apleway Tablets 20 mg	(1) Kowa Company, Ltd. (2) Sanofi K.K.	May 23, 2014
luseogliflozin hydrate Lusefi Tablets 2.5 mg, 5 mg	Taisho Pharmaceutical Co., Ltd.	May 23, 2014
dapagliflozin propylene glycolate hydrate Forxiga Tablets 5 mg, 10 mg	Bristol-Myers K.K.	May 23, 2014
tenofovir disoproxil fumarate Tenozet Tablets 300 mg	GlaxoSmithKline K.K.	May 16, 2014
turoctocog alfa (genetical recombination) Novoeight for Intravenous Infusions 250, 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	May 12, 2014
ferric citrate hydrate Riona Tablets 250 mg	Japan Tobacco Inc.	May 12, 2014
afatinib maleate Giotrif Tablets 20 mg, 30 mg, 40 mg, 50 mg	Nippon Boehringer Ingelheim Co., Ltd.	May 7, 2014
trastuzumab emtansine (genetical recombination) Kadcyla Intravenous Infusions 100 mg, 160 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2014
riociguat Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg	Bayer Yakuhin, Ltd.	April 18, 2014
levocetirizine hydrochloride Xyzal Syrup 0.05%	GlaxoSmithKline K.K.	April 17, 2014
dolutegravir sodium Tivicay Tablets 50 mg	ViiV Healthcare K.K.	April 17, 2014
brentuximab vedotin (genetical recombinatin) Adcetris for Intravenous Infusions 50 mg	Takeda Pharmaceutical Company Limited	April 17, 2014
ipragliflozin l-proline Suglat Tablets 25 mg, 50 mg	Astellas Pharma Inc.	April 17, 2014
tadalafil Zalutia Tablets 2.5 mg, 5 mg	Eli Lilly Japan K.K.	April 17, 2014
tolvaptan Samsca Tablets 7.5 mg, 15 mg, 30 mg*6	Otsuka Pharmaceutical Co., Ltd.	March 24, 2014
fluticasone furoate Allermist 27.5μg 56 metered Nasal Spray*7	GlaxoSmithKline K.K.	March 17, 2014
pazopanib hydrochloride Votrient Tablets 200 mg*8	GlaxoSmithKline K.K.	March 17, 2014
mogamulizumab (genetical recombination) Poteligeo Injections 20 mg*9	Kyowa Hakko Kirin Co., Ltd.	March 17, 2014

*1 An additional indication for “the treatment of patients with refractory nephrotic syndrome (frequently relapsing or steroid-resistant)”

*2 An additional indication for “the treatment of moderate to severe chronic pain”

*3 An additional indication for “the treatment of patients with radically unresectable differentiated thyroid carcinoma”

*4 An additional indication for “the prevention of infection caused by Streptococcus pneumonia serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in elderly patients”

*5 An additional indication for “the treatment of patients with bone giant cell tumour”

*6 An additional indication for “the control of disease progression in patients with autosomal dominant polycystic kidney who already had increased kidney volume and whose kidney volume was further rapidly increasing.” Samsca Tablets 30

mg was launched in May 29, 2014.

*7 An additional administration for “pediatrics”

*8 An additional indication for “the treatment of patients with radically unresectable or metastatic renal cell carcinoma”

*9 An additional indication for “the treatment of patients with relapsed or refractory CCR4-positive peripheral T-cell lymphoma and patients with relapsed or refractory CCR4-positive cutaneous T-cell lymphoma”