Pharmaceuticals and Medical Devices Safety Information

No. 401 May 2023

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 401 May 2023

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.
If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions,

infections associated with drugs or medical devices, or medical device adverse events, please 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.

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)
https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ACE	Angiotensin-converting Enzyme
ADH	Antidiuretic Hormone
ADR	Adverse Drug Reaction
ARB	Angiotensin II Receptor Blockers
CHDF	Continuous Haemodiafiltration
DOA	Dopamine Hydrochloride
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HHV-6	Human Herpes Virus Type 6
JDIIP	Japan Drug Information Institute in Pregnancy
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices
RAS	Renin-angiotensin System
RMP	Risk Management Plan
TEN	Toxic Epidermal Necrolysis

1
Revision of Precautions for Drugs Inhibiting the Renin-angiotensin System

1. Introduction

Drugs inhibiting the renin-angiotensin system (hereinafter referred to as “RAS inhibitors”) include angiotensin-converting enzyme inhibitors (hereinafter referred to as “ACE inhibitors”), angiotensin II receptor blockers (hereinafter referred to as “ARBs”), an angiotensin receptor-neprilysin inhibitor, and a direct renin inhibitor, and they are widely used for the treatment of hypertension, chronic heart failure, etc.

On May 9, 2023, the Ministry of Health, Labour and Welfare (MHLW) issued a notification instructing the marketing authorization holders (MAHs) of RAS inhibitors to add a statement that each of these drugs should be administered to women of child-bearing potential only if the potential therapeutic benefits are considered to outweigh the potential risks and precautions for cases where administration to women of child-bearing potential is necessary. This section will introduce the details of the revision and other relevant information.

2. Background

In the package inserts of RAS inhibitors, pregnant women or women who may be pregnant have been specified in the CONTRAINDICATIONS section, and the precautionary statement that administration of these drugs should be discontinued immediately if pregnancy is detected during administration has been included. These measures were taken in response to the facts that oligohydramnios, foetal or neonatal death, neonatal hypotension, renal failure, hyperkalaemia, and skull hypoplasia, as well as extremity contracture, craniofacial deformation, hypoplastic lung development, etc. presumably associated with oligohydramnios, had been reported in patients treated with ACE inhibitors or ARBs after the second trimester of pregnancy.

In Japan, several cases have been reported in patients who were continuously treated with ACE inhibitors or ARBs even after pregnancy was detected. Adverse events in foetuses possibly associated with a maternal ACE inhibitor or ARB use have also been reported. Therefore, “PMDA Alert for Proper Use of Drugs” No.10 (Adverse Events in Pregnant Women and Foetuses Associated With Use of Angiotensin II Receptor Blockers and Angiotensin-converting Enzyme Inhibitors) was issued in September 2014 by the PMDA to caution against administering these drugs to pregnant women, etc.

However, even after that, similar cases have been intermittently reported. Among them, there have been cases in which the drugs were used in women without recognizing that they were pregnant (the table below).

Fiscal Year	2014	2015	2016	2017	2018	2019	2020	2021	2022
Number of cases in which adverse foetal and neonatal outcomes were suspected to be due to exposure to RAS inhibitors during pregnancy	4	6	4	2	0	4	0	3	1
Among the above cases, the number of the cases for which it was stated in the column of clinical course, etc. of the case report form that pregnancies had not been recognized	2	2	2	2	0	0	0	3	0

*Tabulated using the case reports on adverse drug reactions in Japan reported to the PMDA between April 2014 and December2022

Taking into account these situations, to minimize foetal and neonatal adverse events associated with the use of RAS inhibitors, the MHLW/PMDA concluded that it was necessary to

add precautions for the administration to women of child-bearing potential in addition to the current precautionary statement that these drugs should not be administered to pregnant women or women who may be pregnant, and the MHLW instructed the MAHs of RAS inhibitors to revise “Precautions” on May 9, 2023.

3. Precautions for administration to women of child-bearing potential

For this revision of “Precautions,” the following language was added as precautions for the administration of RAS inhibitors to women of child-bearing potential (also refer to “4. Revisions of Precautions (No.341)” in page 40 of this volume of PMDSI).

- Women of child-bearing potential should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc.
- If administration is considered necessary, attention should be paid to the following points.
  (1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.
  (2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary.
    - This drug can cause foetal and neonatal harm when administered to a pregnant woman.
    - If pregnancy is detected or suspected, the attending physician should be consulted immediately.
    - If pregnancy is planned, the attending physician should be consulted.

4. Others

Taking into account that the notification instructing revision of “Precautions” was issued this time, the PMDA revised “PMDA Alert for Proper Use of Drugs” issued in 2014, and published it on its website (https://www.pmda.go.jp/files/000252467.pdf). Also, the MHLW prepared templates of written information for patients to deepen their understanding about the use of RAS inhibitors. The written information is provided to healthcare professionals through the MAHs of RAS inhibitors. Therefore, healthcare professionals are requested to review “PMDA Alert for Proper Use of Drugs” and their cooperation for proper use of RAS inhibitors, such as distributing the written information to alert female patients, would be appreciated.

5. Closing remark

Healthcare professionals are requested to pay attention to the above points and to avoid administering RAS inhibitors to pregnant women or women of child-bearing potential when the use of these drugs to women of child-bearing potential is considered. Their cooperation for proper use would be appreciated.

PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

No. 10 May 2023

Precautions for Use of the Drugs Inhibiting the Renin-angiotensin System (ACE Inhibitors, ARB, Etc.) in Women of Child-bearing Potential

- The package inserts for drugs inhibiting the renin-angiotensin system (hereinafter referred to as “RAS inhibitors”) caution against administering them to pregnant women, and the precautions have been disseminated to healthcare professionals by “PMDA Alert for Proper Use of Drugs” No.10 issued in September 2014.
- This time, following the revision of package insert to add 2. below, “PMDA Alert for Proper Use of Drugs” No.10 was updated. The reasons for this revision are as follows: Cases have been reported in which these drugs were used continuously during pregnancy and foetal and neonatal adverse events were suspected; in some cases, these drugs were used in women without recognizing that they were pregnant.
- When administering an RAS inhibitor, the following points[*1] should be reviewed, and RAS inhibitors should not be administered to pregnant women.

1. RAS inhibitors should not be administered to pregnant women or women who may be pregnant.

2. The necessity of administering an RAS inhibitor to women of child-bearing potential should be carefully considered. Also, if administration is considered necessary, attention should be paid to the following points.

- The absence of pregnancy should be confirmed prior to and during administration.
- When pregnancy is detected, administration of this drug should be discontinued immediately.
- Patients should be informed that this drug can affect foetuses and neonates, and should be advised repeatedly that they should consult with their attending physician if pregnancy is detected or suspected[*2], or pregnancy is planned.

*1 Precautions common to RAS inhibitors are described in this document. For the details of precautions of each drug, package inserts for each drug can be searched for and viewed on the PMDA website (https://www.pmda.go.jp/) (only available in Japanese).

*2 Delayed menstruation or amenorrhoea, hyperemesis gravidarum (symptoms of morning sickness), continuation of the high-temperature phase in cases where basal body temperature is measured, etc.

●Reports of cases*

- Cases have been intermittently reported in which RAS inhibitors were used during pregnancy and adverse foetal and neonatal outcomes (renal failure, aplasia of skull, lung, and kidney, death, etc.) are suspected, even after 2014 when “PMDA Alert for Proper Use of Drugs” No.10 was issued.
- Among them, there have been cases in which RAS inhibitors had been used since before pregnancy and they were continuously used in women without recognizing that they were pregnant.

Fiscal Year	2014	2015	2016	2017	2018	2019	2020	2021	2022
Number of cases in which adverse foetal and neonatal outcomes were suspected to be due to exposure to RAS inhibitors during pregnancy	4	6	4	2	0	4	0	3	1
Among the above cases, the number of the cases for which it was stated in the column of clinical course, etc. of the case report form that pregnancies had not been recognized	2	2	2	2	0	0	0	3	0

*Tabulated using the case reports on adverse drug reactions in Japan reported to the PMDA between April 2014 and December 2022

Typical case reports

Case 1. Suspected drug: Candesartan cilexetil

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ Age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s Female offspring	Hypertension (diabetes mellitus)	Unknown (approximately 2 years)	Offspring: Cleft lip and palate, skull hypoplasia	
			Day 1 of administration	The mother was diagnosed with diabetes mellitus and hypertension and she was treated with oral administration of metformin and candesartan cilexetil at another hospital.
			Approximately 2 years after administration	The mother was primiparous. Pregnancy was spontaneously achieved. However, she did not recognize her pregnancy. She noticed bloating during the second trimester of pregnancy, and therefore visited the other hospital.
			Approximately 2 years after administration (Day of discontinuation)	Gestational age was estimated to be 33 weeks and 5 days based on the timing of the last menstruation and ultrasound findings. The mother was referred to this hospital for inpatient management. After admission to this hospital, treatment regimens for diabetes mellitus and hypertension were changed to insulin injection and oral administration of methyldopa. Foetal ultrasound during hospitalization showed no sign of oligohydramnios. No other foetal malformation was noted.
			24 days after discontinuation (0 days old)	Labour pain occurred spontaneously at 37 weeks and 1 day gestation. Since decreased foetal heart rate was confirmed before delivery, the mother had a cephalic vaginal delivery using vacuum extraction. The offspring was appropriate-for-dates female with a body weight of 2 436 g. 1-minute Apgar score, 8; 5-minute Apgar score, 9. Umbilical cord arterial blood gas pH, 7.212 Umbilical cord arterial blood gas BE, -7.6 mmoL/L. After birth, respiratory status was stabilized with oxygen administration. The offspring was hospitalized for having been born from the mother with diabetes mellitus. Physical findings at the time of hospitalization: Opening of anterior/posterior fontanel (8 cm × 8 cm) and dehiscence of sagittal suture were observed. While no peculiar face was noted, there were cleft lip and palate. Vitality of the offspring was good. Muscle tightness of the four limbs was well kept without contracture. No hypothyroidism was noted. X-ray images showed skull hypoplasia from the frontal bone to the occipital bone. Ultrasound revealed no apparent sign of malformation in the brain and heart, or intracranial haemorrhage.
			25 days after discontinuation (1 day old)	On head CT images of the offspring, ossified areas of the frontal bone/parietal bone/occipital bone/temporal bone were found to be small and separated.
			28 days after discontinuation (4 days old)	No hypothyroidism was observed in the offspring.
			36 days after discontinuation (12 days old)	Since systemic condition and weight gain of the offspring were good, the offspring was discharged from the hospital.
			3 months after discontinuation (3 months old)	Therapeutic response was good. A head CT showed that cranial ossification progressed compared with that immediately after birth, and cranial osteogenesis was appropriate for 3 months old.
Concomitant drugs: Metformin hydrochloride Note: Shinya Abe, et al. Perinatal Medicine. 2017; 47: 1353-1355.				

Case 2. Suspected drug: Olmesartan medoxomil

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s First child: Female offspring Second child: Male offspring	Moyamoya disease (none)	20 mg (1 year)	Mother: Oligohydramnios Offspring (first child, second child): Pulmonary hypoplasia, foetal kidney enlargement, neonatal kidney enlargement, neonatal proximal renal tubular dysgenesis, neonatal respiratory failure	
			Day 1 of administration (1 year ago)	The mother had been orally taking olmesartan medoxomil 20 mg since 1 year before pregnancy as a treatment of moyamoya disease. Pregnancy was spontaneously achieved. She did not recognize her pregnancy until a family member pointed out that her abdomen became larger. Therefore, she made an initial visit to the obstetrics and gynecology department of hospital A. Gestational age was calculated to be 27 weeks and 2 days. Since the sexes of the foetuses were male and female, it was diagnosed as diamniotic dichorionic twin pregnancy.
			Day of discontinuation (28 weeks and 2 days gestation)	Since both foetuses had oligohydramnios, the mother was referred to a secondary maternity facility (hospital B) at 28 weeks and 2 days gestation. She was admitted to hospital B on the same day. Although oral administration of ARB was discontinued after admission to hospital B, the amniotic fluid volume did not increase. Accordingly, she was urgently transported to this hospital at 30 weeks and 2 days gestation.
			From day of discontinuation to 26 days after discontinuation (28 weeks and 2 days gestation to 32 weeks 0 days gestation)	Transabdominal ultrasound at the time of admission to this hospital showed that the maximum vertical pocket (MVP) for both foetuses was 0 cm. Both kidneys were presented with high echogenicity. TC/AC was measured for multiple times from 28 weeks and 2 days gestation to 32 weeks and 0 days gestation. Minimum TC/AC was 0.73 for the first child and 0.71 for the second child. Pulmonary hypoplasia was suspected in both foetuses. Both kidneys of the first child were enlarged. The right kidney of the first child had an anteroposterior width of 41 mm, transverse width of 21 mm and long diameter of 55 mm (normal anteroposterior width: 22.4±1.7 mm, normal long diameter: 40.6±2.8 mm), and the left kidney had an anteroposterior width of 36 mm, transverse width of 25 mm and long diameter of 53 mm. Both kidneys of the second child were also enlarged. The right kidney of the second child had an anteroposterior width of 36 mm, transverse width of 24 mm and long diameter of 53 mm, and the left kidney had an anteroposterior width of 32 mm, transverse width of 26 mm and long diameter of 53 mm. Bladder with a diameter of 10 mm was observed in both foetuses.
			26 days after discontinuation (32 weeks 0 days gestation)	Ultrasound at 31 weeks and 1 day gestation showed no amniotic cavity for both foetuses; however, an amniotic cavity with the MVP exceeding 1 cm was confirmed for the first time at 32 weeks and 0 days gestation (approximately 5 weeks after discontinuation of ARB).
			30 days after discontinuation (32 weeks and 4 days gestation)	Labour pain occurred. Since the first child was in breech presentation, an emergency caesarean section was performed. Neonatal findings (first child): Sex, female 1-minute Apgar score, 4; 5-minute Apgar score, 6 Umbilical cord arterial blood pH, 7.129 Neonatal findings (second child): Sex, male 1-minute Apgar score, 6; 5-minute Apgar score, 7 Umbilical cord arterial blood pH, 7.175 The offspring were intubated and placed on ventilator management after birth. However, respiratory failure was serious, and there was no urine output. Both offspring died 15 hours after birth. Autopsy (kidneys): The first child had the right kidney with a weight of 20.0 g and left kidney with a weight of 20.0 g. The second child had the right kidney with a weight of 22.5 g and left kidney with a weight of 27.0 g. Compared to a normal weight of 15.0±4.4 g, the kidneys of both offspring were remarkably enlarged. Histological investigation (kidneys): Poor differentiation and decreased number of proximal/distal renal tubules (especially proximal renal tubules) due to poor development of these renal tubules were noted. CD10 immunostaining of glomerular epithelial cells (glomerular foot process)/proximal renal tubules showed significant decrease in the number of proximal renal tubules. Autopsy (lungs): The first child had the right lung with a weight of 11.5 g and left lung with a weight of 12.5 g. The second child had the right lung with a weight of 12.0 g and left lung with a weight of 14.5 g. These weights were less than 50% of the normal weight of 31.2±9.0 g for neonates delivered after 32 weeks gestation. Histological investigation (lungs): As for maturity of the lungs, the lungs of both offspring had developed to terminal sac period (equivalent to that of a foetus at 26 weeks to 38 weeks gestation). However, radial alveolar count (2 for the first child and 1 for the second child) was significantly smaller than the normal range of 4 to 5 for a full-term neonate. Since there was no tumour in pleural cavity or diaphragmatic hernia, it was diagnosed as pulmonary hypoplasia due to oligohydramnios.
Suspected concomitant drugs: None Note: Daisuke Saito, et al. Kagoshima Journal of Obstetrics and Gynecology. 2021; 29: 49-54.				

Case 3. Suspected drug: Valsartan

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s Female offspring (0 days old)	Mother; hypertension (Mother; asthma, gastrooesophageal reflux disease, upper abdominal pain) (Offspring; low birth weight baby, neonatal respiratory distress syndrome)	40 mg (391 days)	Offspring: Skull hypoplasia, neonatal renal impairment	
			Day of administration	Since home blood pressure was not controlled, administration of valsartan was initiated. Vonoprazan fumarate was also taken from Day 202 to Day 209 of administration. Rabeprazole sodium was switched to esomeprazole magnesium hydrate once. On Day 300 of administration, esomeprazole magnesium hydrate was switched back to rabeprazole sodium. The mother had received a prescription of theophylline for asthma, and loxoprofen sodium hydrate and teprenone for low back pain.
			Date unknown	The mother consulted with an internist after feeling foetal movement, but it was judged to be intestinal movement.
			Day 391 of administration (Day of discontinuation)	The mother took a self-pregnancy test. After confirming a positive result, she visited an obstetrician. Blood pressure was 184/123 mmHg. She was severely obese, weighing 117 kg, an increase of 27 kg since her last pregnancy. Since HbA1c was relatively high at 6.1%, glycosuria during pregnancy was suspected. Amniotic fluid volume was normal. Administration of valsartan and amlodipine besilate was discontinued, and was switched to nifedipine.
			3 days after discontinuation (0 days old)	The offspring was delivered by caesarean section due to hypertension and breech presentation. Gestational age was 36 weeks and 4 days, birthweight was 2 336 g, and Apgar score was 7/7. The offspring was hospitalized at the neonatal department for having respiratory disorder and having been born from a mother who was taking an angiotensin II receptor blocker. Renal disorder and skull hypoplasia were observed. The skull was thin, and the anterior fontanel (5 ×4.5 cm) and the posterior fontanel (3 × 3 cm) were widely open. Tongue-shaped bone defect at the distal end of the right long bone was noted. Furthermore, neonatal idiopathic respiratory distress syndrome was diagnosed. Endotracheal intubation was performed, and pulmonary surfactant preparation (120 mg/kg) was administered. Ventilator management was necessary. Midazolam was used (0.1 mg/kg/day) for sedation.
			4 days after discontinuation (1 day old)	Furosemide (1 mg/kg) and normal saline solution (5 mL/kg) were administered twice for oliguria. Due to a high phosphorus level and a low calcium level, administration of calcium gluconate hydrate was initiated (3 mL/kg/day).
			6 days after discontinuation (3 days old)	Uric acid and creatinine levels increased. Serum sodium level showed a decreasing tendency due to polyuria. Volume of infusion fluid was increased and 10% NaCl supplementation was initiated. Oral administration of furosemide (1 mg/kg/day) and spironolactone (1 mg/kg/day) was initiated. Blood pressure was stable at 70/40 mmHg.
			14 days after discontinuation (11 days old)	Administration of calcium gluconate hydrate was discontinued.
			15 days after discontinuation (12 days old)	Artificial ventilation was discontinued, and extubation was performed. Administration of midazolam was completed.
			16 days after discontinuation (13 days old)	Oxygen administration was discontinued, and positive pressure ventilation was initiated. Serum creatinine and uric acid levels were normalized. Fractional excretion of sodium (FENa) and renal failure index (RFI) were still high.
			17 days after discontinuation (14 days old)	Administration of furosemide and spironolactone was completed.
			19 days after discontinuation (16 days old)	Positive pressure ventilation was completed.
			27 days after discontinuation (24 days old)	Administration of 10% NaCl was completed.
			29 days after discontinuation (26 days old)	Urinary NAG level was still high at 24.1 IU/L. Serum osmolality and urine osmolarity were normal. PCO_2 was normalized. The offspring was fed concomitantly with injection of liquid nutrition. Since urine output volume was slightly high, the offspring was fed with a slightly high volume of milk. MRI: There was no apparent abnormality in the head. Lobes in both kidneys were relatively large. Kidney ultrasound: Glomerular structures were not clearly visible.
			43 days after discontinuation (40 days old)	FENa and RFI were normalized. Urinary NAG level was still high. Total amount of milk was orally fed, and urine output volume became stabilized. Weight gain was poor. Milk for treatment was used due to milk allergy. Subsequent weight gain was good.
			49 days after discontinuation (46 days old)	The offspring recovered from renal disorder, but did not recover from skull hypoplasia.

Laboratory test value

	0 days old	3 days old	5 days old	11 days old	26 days old	40 days old
Serum creatinine (mg/dL)	0.53	1.49	1.21	0.52	0.24	0.21

Concomitant drugs: Amlodipine besilate, nifedipine, vonoprazan fumarate, esomeprazole magnesium hydrate, rabeprazole sodium, theophylline, loxoprofen sodium hydrate, teprenone

Case 4. Suspected drug: Azilsartan

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s Offspring (unknown)	Hypertension (diabetes mellitus, obesity)	20 mg (2 days) ↓ 40 mg (16 days)	Mother: None Mother's medical history, predisposition and others: Smoking Offspring: Neonatal renal failure, neonatal hypotension, acute kidney injury, hypotension, cerebral ischaemia, meconium aspiration syndrome, pulmonary oedema, respiratory failure, hypoxic-ischaemic encephalopathy	
			Before administration	Gravida 1, para 1, smoker, no alcohol consumption The mother did not recognize her pregnancy because her menstrual cycles had been irregular.
			Day 1 of administration	The mother experienced aggravation of difficulty breathing 1 month before delivery. Hypertension, cardiac failure and diabetes mellitus were diagnosed. Oral administration of azilsartan (20 mg/day), nifedipine, azosemide, spironolactone, and empagliflozin was initiated.
			Day 3 of administration	The dose of azilsartan was increased (40 mg/day).
			Day of discontinuation (Day 17 of administration) (0 days old)	Abdominal pain and genital haemorrhage were observed. As pregnancy was discovered, delivery was performed. Administration of azilsartan was discontinued (last administration on that date). <Clinical course of the offspring> New Ballard score was 38 points, and maturity of the offspring was equivalent to that of 38 weeks gestation. Meconium stain and laboured respiration were observed, and meconium aspiration syndrome was suspected. However, laboured respiration gradually improved, and oxygenation was maintained. In a room air setting, ampicillin/aztreonam (ABPC/AZT) was administered. At the time of admission, blood pressure was 60/29 (40) mmHg (drug-induced hypotension in neonate). Blood Cys-C level was 7.07 mg/L, Cre level was 1.33 mg/dL, and BUN was 19 mg/dL. Abdominal ultrasound revealed increased echogenicity of the renal cortex and disruption of renal blood flow in the diastolic phase (acute renal failure in neonate). It was considered to be attributed to oral administration of azilsartan in the mother. However, no electrolyte abnormality or metabolic acidosis was observed. Maintenance infusion of 10% glucose fluid was performed, and the clinical course was followed up.
			-	Anuria was still persisting 24 hours after birth. Since hyperkalaemia occurred, administration of furosemide and glucose-insulin therapy was initiated. Pulmonary oedema developed 36 hours after birth. The offspring was placed on directional positive airway pressure (DPAP). Administration of dopamine hydrochloride (DOA) 4 gamma and antidiuretic hormone (ADH) 0.001 U/kg/min was initiated to increase blood pressure and improve renal blood flow.
			3 days after discontinuation	Diuresis was not achieved. Cre and BUN increased to 4.43 mg/dL and 28 mg/dL, respectively. Intubation was performed. Ventilator management and continuous haemodiafiltration (CHDF) were initiated.
			6 days after discontinuation	Spontaneous urination was gradually observed, thereafter. Therefore, CHDF was discontinued. Neonatal acute renal failure and neonatal drug-induced hypotension were recovering.
			10 days after discontinuation	After discontinuation of CHDF, spontaneous urination was maintained. Accordingly, DOA/ADH was completed.
			15 days after discontinuation	On head MRI images, laminar necrosis of the left cerebral hemisphere and hypointense areas in deep white matter around the anterior horns of both lateral ventricles (cerebral ischaemia in neonate) were observed. They were considered to be signs of hypoxic encephalopathy. The offspring did not recover from cerebral ischaemia in neonate.
			16 days after discontinuation	During the clinical course, the offspring sometimes presented with myoclonus-like limb tremor and pedaling-like motion. However, recorded brain waves showed no abnormal findings.
			18 days after discontinuation	Feeding and weight gain were good. No metabolic acidosis was noted. The offspring was discharged from the hospital with a body weight of 3 414 g.
			Date unknown	Clinical outcomes of meconium aspiration syndrome, pulmonary oedema, respiratory failure and hypoxic encephalopathy were unknown.

Laboratory test value

	Day of discontinuation (0 days old)	3 days after discontinuation	13 days after discontinuation	18 days after discontinuation
Blood pressure (mmHg)	60/29, 60/40	75/55	70/45	-
Cys-C (mg/L)	7.07	-	-	-
Blood creatinine (mg/dL)	1.33, 2.04	4.43	2.01	-
BUN (mg/dL)	15, 19	28	15	-
Body weight (kg)	2.6	2.6	2.6	3.414

Concomitant drugs: Nifedipine, azosemide, spironolactone, empagliflozin, lansoprazole

•RAS inhibitors approved in Japan

(As of April, 2023)

Angiotensin II receptor blockers (ARBs)

Non-proprietary name	Brand name
Azilsartan	Azilva and the others
Irbesartan	Avapro, Irbetan, and the others
Olmesartan medoxomil	Olmetec and the others
Candesartan cilexetil	Blopress and the others
Telmisartan	Micardis and the others
Valsartan	Diovan and the others
Losartan potassium	Nu-Lotan and the others
Azilsartan/ amlodipine besilate	Zacras, ZilMlo
Irbesartan/ amlodipine besilate	Aimix, Iluamix
Irbesartan/ trichlormethiazide	Irtra
Olmesartan medoxomil/ azelnidipine	Rezaltas
Candesartan cilexetil/ amlodipine besilate	Unisia, Camshia
Candesartan cilexetil/ hydrochlorothiazide	Ecard, Cadethia
Telmisartan/ amlodipine besilate	Micamlo, Teramuro
Telmisartan/ amlodipine besilate/ hydrochlorothiazide	Micatrio
Telmisartan/ hydrochlorothiazide	Micombi, Telthia
Valsartan/ amlodipine besilate	Exforge, Amvalo
Valsartan/cilnidipine	Atedio
Valsartan/ hydrochlorothiazide	Co-Dio, Valhydio
Losartan potassium/ hydrochlorothiazide	Preminent, Losarhyd

Angiotensin-converting enzyme inhibitors (ACE inhibitors)

Non-proprietary name	Brand name
Alacepril	Cetapril and the others
Imidapril hydrochloride	Tanatril and the others
Enalapril maleate	Renivace and the others
Captopril	Captoril and the others
Temocapril hydrochloride	Acecol and the others
Delapril hydrochloride	Adecut
Trandolapril	Odric and the others
Benazepril hydrochloride	Cibacen and the others
Perindopril erbumine	Coversyl and the others
Lisinopril hydrate	Zestril, Longes, and the others

Direct renin inhibitor

Non-proprietary name	Brand name
Aliskiren fumarate	Rasilez

Angiotensin receptor-neprilysin inhibitor

Non-proprietary name	Brand name
Sacubitril valsartan sodium hydrate	Entresto

The Japan Drug Information Institute in Pregnancy (JDIIP) in the National Center for Child Health and Development 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.

JDIIP:
http://www.ncchd.go.jp/kusuri/index.html
(only in Japanese)

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 Adverse Drug Reaction/infection cases reported in accordance with the PMD Act.
- 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 responsibility on them, but is provided to promote the proper use of the drugs.
- This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Access to the most up to date safety information is available via the PMDA medi-navi.

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The Survey Results on the Status of Acquisition, Communication, and Use of Drug Safety Information at Hospitals and Pharmacies and Desirable Directions

1. Introduction

The MHLW and the PMDA have been implementing safety measures, such as revision of Precautions in package inserts, etc., based on the reported information on adverse reactions to cooperatively ensure proper use of drugs and medical devices. Information necessary for the implementation of safety measures has been provided by the MHLW, the PMDA, the pharmaceutical companies, etc. to medical institutions through various routes. It is important to properly communicate the information to the related parties so that they can use it in clinical practice.

Since FY 2010, the PMDA has been conducting surveys to understand the status of acquisition, communication, and use of safety information at medical institutions, etc. and to consider measures to promote the use of safety information for the purpose of ensuring steady implementation of the safety measures taken and further patient safety.

The current FY 2022 survey focused on, among others, the impact of the digitization of package inserts, which was stipulated by the amendment of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960; hereinafter referred to as the “PMD Act”) enforced in August 2021, on the acquisition and communication of drug safety information and the status of use of risk communication tools such as the Risk Management Plan (hereinafter referred to as the “RMP”). This article introduces 1) acquisition of information related to the digitization of package inserts, 2) the status of understanding and use of the RMP, which was identified as an issue in the previous survey (the FY 2017 survey), and 3) the survey results on comprehensive acquisition of important information and the discussion (“desirable directions”).

2. Surveys in FY 2022 (hospital and pharmacy surveys)

(1) Methods and contents of the survey

The duration, methods, main contents, etc. of the surveys conducted in FY 2022 (the survey of hospitals is hereinafter referred to as the "hospital survey," and the survey of pharmacies is hereinafter referred to as the "pharmacy survey”) are as shown in Table 1.

The "Review Committee for the Survey on the Status of Acquisition, Communication, and Use of Drug Safety Information at Medical Institutions, etc." (Chairperson, Masahiro Hayashi, Regulatory Affairs Specialist at Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital), which consists of experts on the operations of physicians and pharmacists and on drug information, was established within the PMDA to hear their opinions on the surveys.

Table 1. Outline of the surveys

	Hospital survey	Pharmacy survey
Duration	June 17 to July 29, 2022	
Hospitals/pharmacies surveyed	40% of hospitals nationwide (3 282 institutions)	5% of health insurance pharmacies nationwide (3 030 institutions)
Methods	Survey forms were sent to the drug safety manager by post.	Survey forms were sent to the supervising pharmacist or the DI personnel by post.
	Multiple choice or open-ended questions	
	Respondents either completed the web questionnaire or returned the paper questionnaire.	
Main contents	・ Means of acquiring and communicating drug safety information ・ Status of application usage, etc. related to the digitization of package inserts ・ The status of understanding and use of the RMP and the Manuals for Management of Individual Serious Adverse Drug Reactions ・ The status of use of the PMDA Medi-navi and the service to create My Drug List for Safety Update	

(2) Outline of survey respondent facilities

A total of 1 441 facilities (43.9%) responded to the hospital survey, and 2 103 facilities (69.5%) responded to the pharmacy survey. The overview of the respondent facilities is shown in Figure 1 and 2.

Figure 1: Number of beds [hospitals]

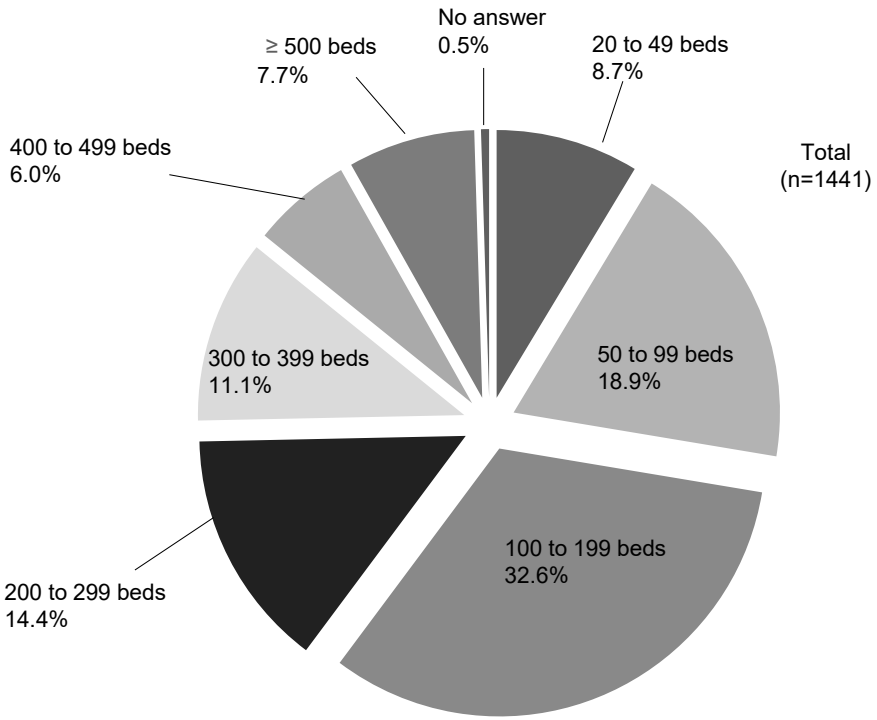


Figure 2-1: Number of prescriptions processed [pharmacies]

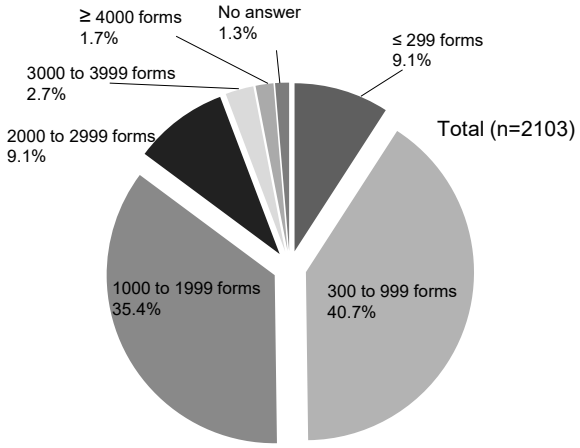
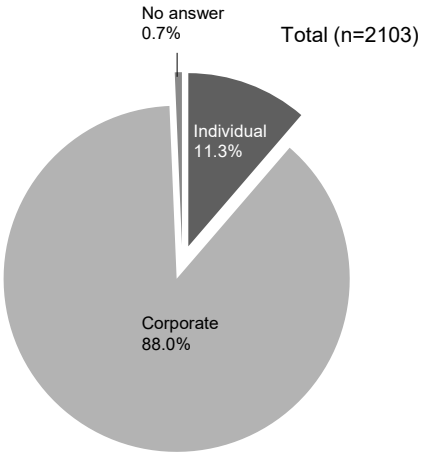


Figure 2-2: Management body [pharmacies]



* Number of prescriptions processed in May 2022 or in the most recent month

(3) Summary of survey results

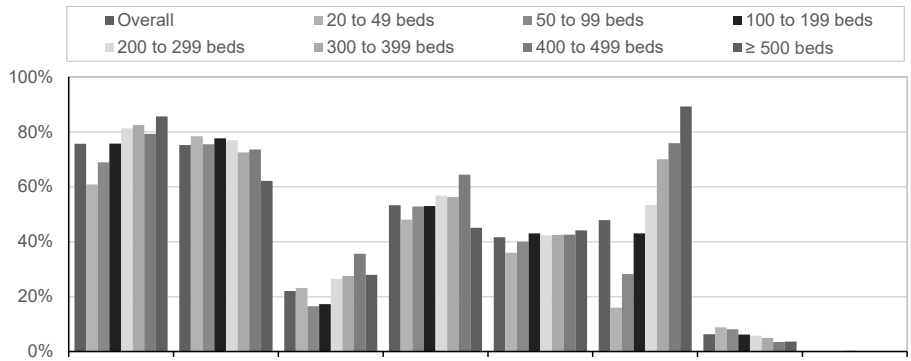
The results of the current surveys (surveys in FY 2022) are summarized below. The results of the previous surveys (surveys in FY 2017) are shown for comparison.

1) Acquisition of the latest information related to the digitization of package inserts

The problem with the traditional means of providing information in paper package inserts is that the latest information is not always provided to healthcare professionals because, for example, some products in the inventory include unrevised package inserts. With the enforcement of the amended PMD Act in August 2021, the method of providing drug safety information has significantly changed. As a general rule, the latest package insert information will be available on the PMDA website for electronic browsing.

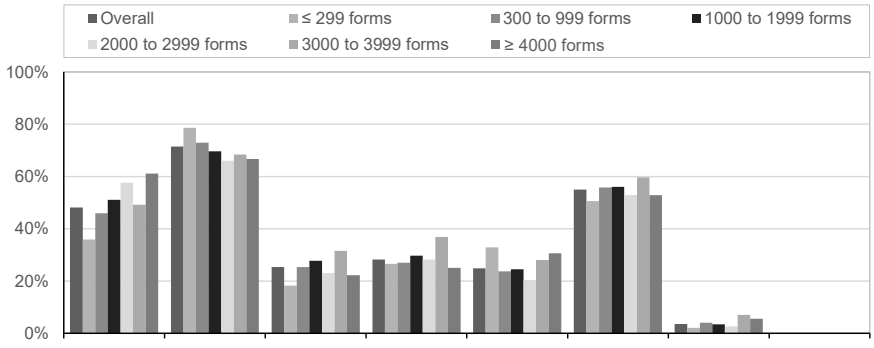
When asked about the means of browsing the latest package insert information (multiple choices allowed), 75.6% of hospitals and 48.1% of pharmacies said they would visit the PMDA website, and approximately a half (47.9% and 55.0%, respectively) of the respondent facilities said they would use their in-house system such as the electronic medical record system and receipt computer system. Hospitals with a large number of beds tended to use their in-house system such as the electronic medical record system (Figure 3). While many facilities said they would also refer to paper package inserts (75.2% of hospitals and 71.4% of pharmacies), those relying solely on paper package inserts were few (1.7% and 2.7%, respectively).

Figure 3-1: Method of browsing the latest package insert information (multiple choices allowed) [hospitals]



Number of beds	Number of respondent facilities	Search the PMDA website		Read the paper package insert if included with the product.		Read the barcode (GS1 barcode) of the product using an application such as Tenbun Navi.		Check the website of the pharmaceutical company		Acquire information from the medical representatives (MRs) or the marketing specialists (MS)		Use the in-house system such as electronic medical record system.		Other		No answer	
			(%)		(%)		(%)		(%)		(%)		(%)		(%)		(%)
Overall	1441	1090	75.6	1084	75.2	317	22.0	768	53.3	599	41.6	690	47.9	90	6.2	1	0.1
20 to 49 beds	125		60.8		78.4		23.2		48.0		36.0		16.0		8.8		-
50 to 99 beds	273		68.9		75.5		16.5		52.7		39.9		28.2		8.1		-
100 to 199 beds	470		75.7		77.7		17.2		53.0		43.0		43.0		6.2		0.2
200 to 299 beds	208		81.3		76.9		26.4		56.7		42.3		53.4		5.8		-
300 to 399 beds	160		82.5		72.5		27.5		56.3		42.5		70.0		5.0		-
400 to 499 beds	87		79.3		73.6		35.6		64.4		42.5		75.9		3.4		-
≥ 500 beds	111		85.6		62.2		27.9		45.0		44.1		89.2		3.6		-

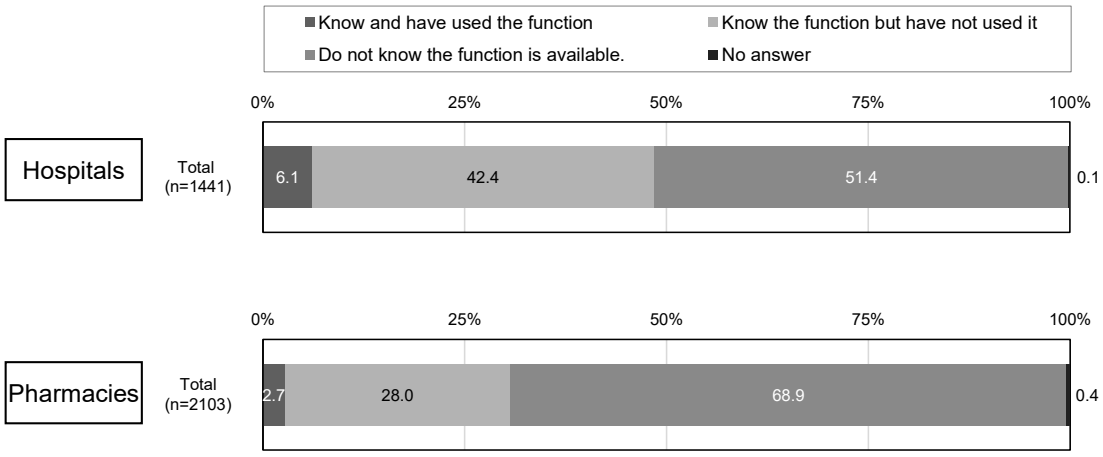
Figure 3-2: Method of browsing the latest package insert information (multiple choices allowed) [pharmacies]



Number of prescriptions processed	Number of respondent facilities	Search the PMDA website		Read the paper package insert if included with the product.		Read the barcode (GS1 barcode) of the product using an application such as Tenbun Navi.		Check the website of the pharmaceutical company		Acquire information from the medical representatives (MRs) or the marketing specialists (MS)		Use the in-house system such as receipt computer system		Other		No answer	
			(%)		(%)		(%)		(%)		(%)		(%)		(%)		(%)
Overall	2103	1012	48.1	1502	71.4	533	25.3	594	28.2	522	24.8	1156	55.0	76	3.6	0	-
≤ 299 forms	192		35.9		78.6		18.2		26.6		32.8		50.5		2.1		-
300 to 999 forms	855		46.0		73.0		25.4		27.0		23.7		55.8		4.0		-
1000 to 1999 forms	744		51.1		69.6		27.7		29.7		24.5		56.0		3.4		-
2000 to 2999 forms	191		57.6		66.0		23.0		28.3		20.4		52.9		2.6		-
3000 to 3999 forms	57		49.1		68.4		31.6		36.8		28.1		59.6		7.0		-
≥ 4000 forms	36		61.1		66.7		22.2		25.0		30.6		52.8		5.6		-

In line with the enforcement of the amended PMD Act, the PMDA has developed the bulk download function of package inserts of prescription drugs (provided through the service to create My Drug List for Safety Update, an optional function of the PMDA Medi-navi) to provide a means to browse package insert information at the facilities when the Internet connection is unavailable, such as at the time of a disaster. To the question about the status of recognition and use of this function, more than a half of the respondent facilities (51.4% of hospitals and 68.9% of pharmacies) said they did not know about it. Only a few facilities (6.1% and 2.7%, respectively) have used the function (Figure 4).

Figure 4: Recognition of bulk download function of package insert



2) Understanding and use of the RMP

Sharing drug-related risks among healthcare professionals, pharmaceutical companies, administrative organs, and patients based on the latest information (risk communication) is important to minimize the risks of drugs. The RMP, a risk communication tool, is a document summarizing a flow of risk management from the development stage to the post-marketing stage. It has become mandatory for pharmaceutical companies to prepare RMPs for products for which an application for marketing approval has been or will be filed on or after April 1, 2013. Implementation of the RMP is a condition for marketing approval. In addition to the regular risk minimization activities based on the RMP, the RMP materials (materials prepared and provided as part of the additional risk minimization activities) summarize information that needs to be provided to healthcare professionals and patients to ensure safety based on the characteristics of individual drug products.

To the question about the status of understanding of the RMP, 54.4% of hospitals (48.2% in the previous survey) and 25.2% of pharmacies (17.4% in the previous survey) answered they understood what the RMP was (understand well or understand to some extent). The result was not significantly different from the previous surveys (Figure 5).

Of these, 61.2% of hospitals and 44.3% of pharmacies have used the RMP. These facilities account for 33.3% and 11.2%, respectively, of all respondent facilities. The result was not significantly different from the previous surveys (24.4% and 6.9%, respectively, of all respondent facilities). In addition, 53.7% of hospitals and 38.2% of pharmacies have used the RMP materials in their operations, accounting for 29.2% and 9.6%, respectively, of all respondent facilities.

The facilities that have never used the RMP or the RMP materials gave their reasons for not using them. They have never used the RMP because they have had no opportunity to use it or because other information sources such as package inserts and interview forms have been sufficient. The reasons for not using the RMP materials included having had no opportunity to use them and not knowing how to use them specifically (Table 2 and 3).

Figure 5: Status of understanding of the RMP

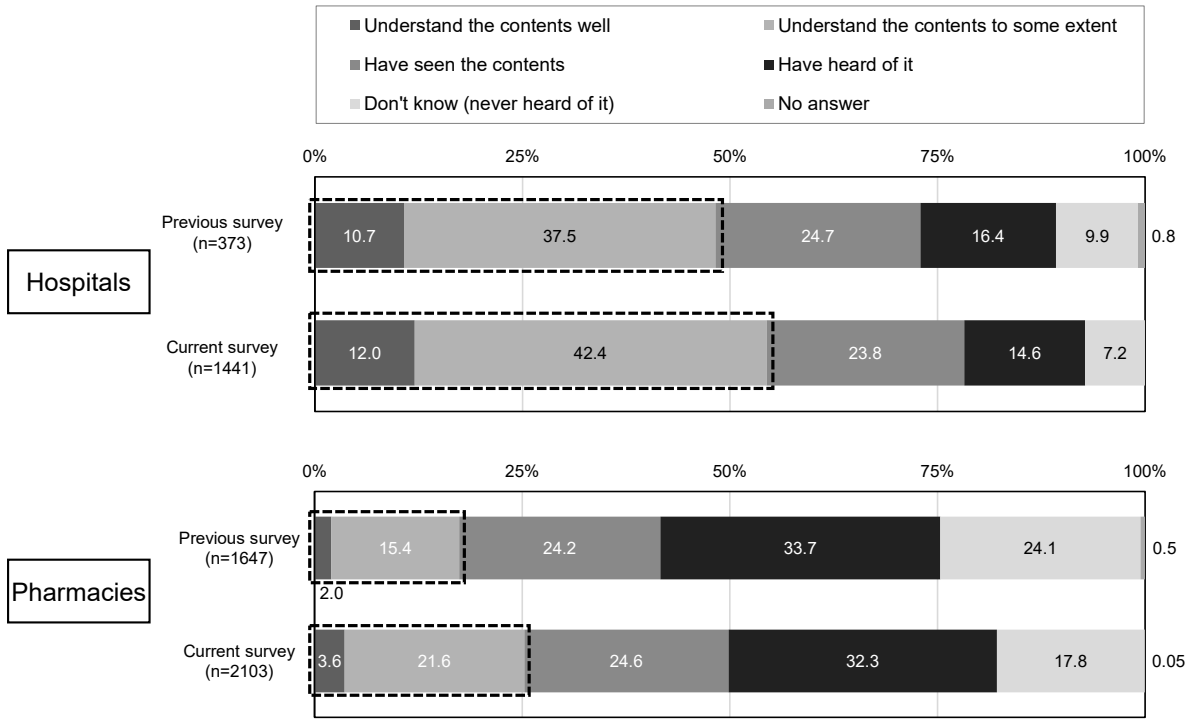


Table 2: Reasons for not using the RMP (multiple choices allowed)

[Hospitals]
1. No opportunity to use it (50.0%)
2. Other information sources such as package inserts and interview forms are sufficient. (43.4%)
3. Not knowing how to use it specifically (31.3%)

[Pharmacies]
1. No opportunity to use it (49.3%)
2. Other information sources such as package inserts and interview forms are sufficient. (43.6%)
3. Not knowing how to use it specifically (27.7%)

Table 3: Reasons for not using the RMP materials (multiple choices allowed)

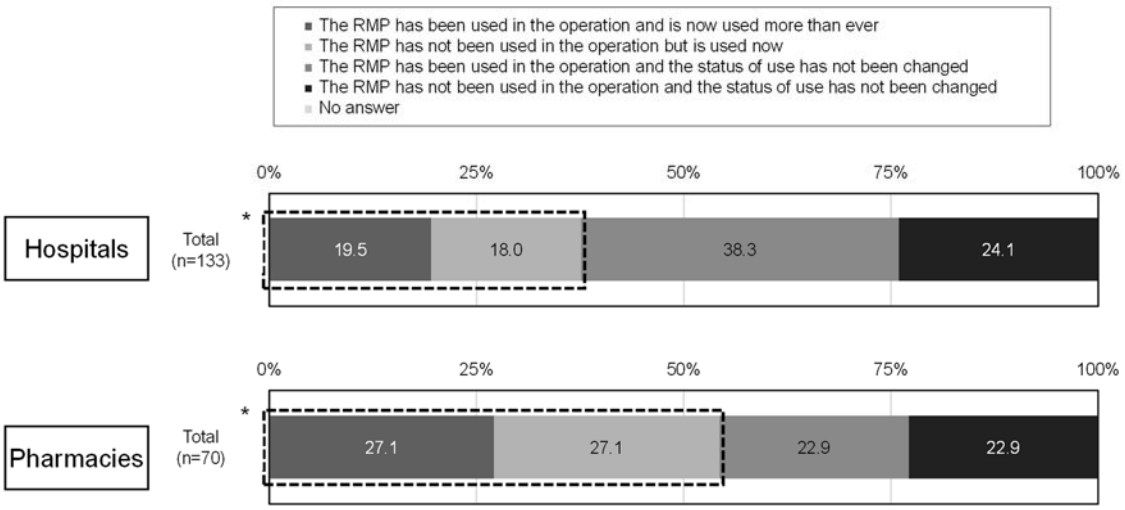
[Hospitals]
1. No opportunity to use them (50.8%)
2. Not knowing how to use them specifically (36.1%)
3. The contents of the materials are difficult for patients. (15.8%)
4. Difficult to understand which information in the materials is important. (14.4%)
5. No materials available at hand (13.6%)

[Pharmacies]
1. No opportunity to use them (45.4%)
2. Not knowing how to use them specifically (29.9%)
3. The contents of the materials are difficult for patients. (21.9%)
4. Difficult to understand which information in the materials is important (16.4%)
5. Unable to identify the RMP materials (15.4%)

Based on the previous surveys showing an insufficient understanding and use of the RMP, the PMDA has created and published e-learning videos explaining the RMP and showing examples of actual use. An assessment of the effect of watching the videos showed the use of the RMP was further promoted at 37.5% of hospitals and 54.2% of pharmacies (Figure 6).

Figure 6: Changes in the status of use of the RMP after watching the videos

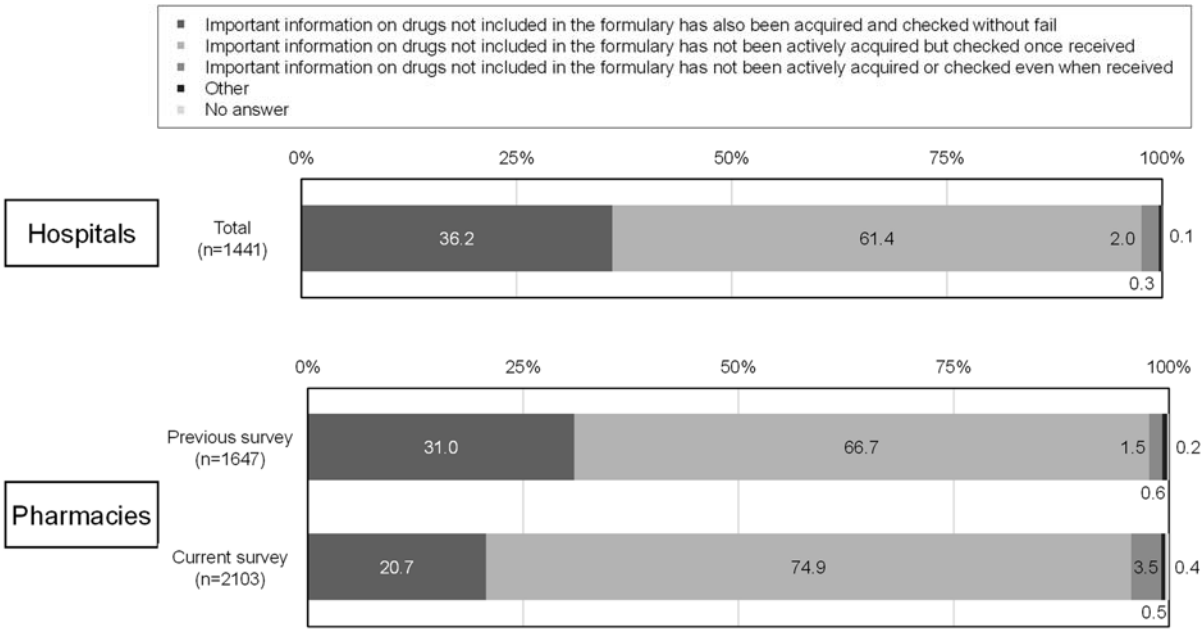
(*Subjects: Institutions that answered they knew and have watched the videos)



3) Comprehensive acquisition of important information

Knowledge of drugs not included in the formulary may be required when, for example, following up patients who take drugs prescribed by other medical institution(s). An assessment of the status of acquiring important information (e.g., Information on Proper Use) on drugs not included in the formulary showed only 36.2% of hospitals and 20.7% of pharmacies had been reliably acquiring such information (Figure 7). This survey item was also assessed in the previous pharmacy survey (31.0%). The current survey showed a lower percentage.

Figure 7: Status of acquiring important information on drugs not included in the formulary



(4) Discussion ("desirable directions")

● Acquisition of the latest drug safety information

The results of the current survey showed that in-house systems such as the electronic medical record system and receipt computer system were widely used, in addition to the PMDA website, to acquire and browse the latest package insert information. Only a few facilities rely on paper media alone. The electronic information stored in the in-house system, etc. may not always be up to date. Therefore, it is important to keep in mind the frequency of the data update in the system, etc. when using the information. Continuous adjustment and maintenance of the system are encouraged to ensure acquisition of the latest information at all times. Healthcare professionals are requested to consider using the bulk download function of package inserts (an optional service of the PMDA Medi-navi) offered by the PMDA as a means to browse package insert information at the facilities when the Internet connection is unavailable, such as at the time of a disaster.

Ensure constant adjustment and maintenance of the system to acquire the latest information at all times depending on the situation at your facilities. Using the bulk download function of package inserts provided by the PMDA is strongly encouraged to prepare for disasters, etc.

● To promote the utilization of drug safety information

The RMP is a document summarizing particularly important information related to a series of risks obtained in the development stage and the post-marketing stage. Development and implementation of the RMP is an approval condition for marketing approval of a drug, and use of the RMP is essential as part of safety measures. It has been approximately 10 years since the introduction of the RMP and several years since the previous surveys. The current surveys found the understanding and use of the RMP and the RMP materials have not improved much since the previous survey. The possible reason is that the understanding of the positioning of the RMP and the RMP materials has not been advanced, and it is considered an important issue to be addressed. Risk minimization activities such as providing information necessary to reduce or

avoid risks and establishing conditions of use and pharmacovigilance activities such as collection of information necessary to identify risks or to further reduce risks, as well as other activities, are described in the RMP. In addition to "Important Identified Risks," the RMP also lists risks under evaluation which are not included in the package inserts as "Important Potential Risks" and "Important Missing Information" where appropriate. The information will be helpful for healthcare professionals when determining the necessity of submitting an adverse reaction report, etc. The RMP materials summarize the information that needs to be provided to healthcare professionals and patients to ensure safety in addition to the usual information provided in package inserts, etc. The PMDA has developed and published e-learning videos as one of the activities to promote understanding of the RMP. Unfortunately, the e-learning videos are still not well known among healthcare professionals. However, the survey results showed watching the videos will promote the use of the RMP. Those who have not watched the e-learning videos that were developed and published by the PMDA are encouraged to do so to deepen their understanding.

Deepen your understanding of the importance of the RMP and the RMP materials and proactively use them.
You can watch the e-learning videos by scanning the QR code on the right (only in Japanese).

● Comprehensive acquisition of important information

It is important that information on Proper Use, Yellow Letters, Blue Letters, instructions for revision of Precautions, etc. is acquired in a timely manner without fail and used to develop early safety measures, regardless of whether or not the drug is included in the formulary. For example, "Information on Proper Use" is issued to ensure the proper use when similar events repeatedly occur despite the precautions already provided in the package insert, etc. The PMDA Medi-navi distributes important information to all registered e-mail addresses with the word [Important] in the e-mail subject line. Registration of your e-mail address is encouraged as a means to comprehensively acquire important information.

Acquire important information comprehensively. Using the PMDA Medi-navi is strongly encouraged.

3. Conclusion

It is essential for healthcare professionals to provide information to patients using the RMP materials and to report adverse reactions based on "Important Potential Risks" and "Important Missing Information" described in the RMP in order to ensure a continual cycle of safety measures and constant drug risk minimization. Also, it is essential for pharmaceutical companies to collect missing information through drug use-results surveys, etc. Healthcare professionals are encouraged to understand the characteristics, the significance, and the purpose of various safety information such as the RMP and the RMP materials and to take advantage of the latest information in their daily practice. This article presents part of the results of the surveys conducted in FY 2022. Other survey results and reports are published on the PMDA website. Utilize the survey results and the “desirable directions” (refer to the URL shown below) to acquire, communicate, and use drug safety information appropriately.

Continuous understanding and cooperation would be appreciated to further ensure patient safety.

[Survey on the status of acquisition, communication, and use of drug safety information at medical institutions, etc.]
https://www.pmda.go.jp/safety/surveillance-analysis/0010.html (only in Japanese)
<Hospital survey>
- Desirable directions (2-page version): https://www.pmda.go.jp/files/000251426.pdf (only in Japanese)
- Key survey results and desirable directions: https://www.pmda.go.jp/files/000251427.pdf

(only in Japanese)
- Survey results report (all results): https://www.pmda.go.jp/files/000251428.pdf (only in Japanese)

<Pharmacy survey>
- Desirable directions (2-page version): https://www.pmda.go.jp/files/000251429.pdf (only in Japanese)
- Key survey results and desirable directions: https://www.pmda.go.jp/files/000251430.pdf (only in Japanese)
- Survey results report (all results): https://www.pmda.go.jp/files/000251431.pdf (only in Japanese)

<Reference information>

The risk communication tools such as the RMP covered in the current surveys are available on the following pages of the PMDA website. Use of the risk communication tools is encouraged for the safety management of drugs, etc. at your facilities when making decisions on formulary adoption or giving medication guidance to patients. The RMP e-learning videos can also be accessed on the same webpage.

[Risk Management Plan (RMP)]
https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0002.html (only in Japanese)

[Manuals for Management of Individual Serious Adverse Drug Reactions (for Healthcare Professionals)]
https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html (only in Japanese)

Registration to the PMDA Medi-navi, a useful tool for information collection, can be made on the following webpage. Registration and use of the PMDA Medi-navi is strongly encouraged.

[PMDA Medi-navi]
https://www.pmda.go.jp/safety/info-services/medi-navi/0007.html (only in Japanese)

Registration to both the PMDA Medi-navi and the service to create My Drug List for Safety Update (an optional function) is required to use the bulk download function of package inserts of prescription drugs.

[Service to create My Drug List for Safety Update and bulk download service for package inserts of prescription drugs]
https://www.pmda.go.jp/safety/info-services/medi-navi/0012.html (only in Japanese)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated May 9, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1

·Angiotensin-converting enzyme inhibitors
[1] Alacepril
[2] Imidapril hydrochloride
[3] Enalapril maleate
[4] Captopril
[5] Temocapril hydrochloride
[6] Delapril hydrochloride
[7] Trandolapril
[8] Benazepril hydrochloride
[9] Perindopril erbumine
[10] Lisinopril hydrate
·Preparations containing angiotensin II receptor blocker
[1] Azilsartan
[2] Irbesartan
[3] Olmesartan medoxomil
[4] Candesartan cilexetil
[5] Telmisartan
[6] Valsartan
[7] Losartan potassium
[8] Azilsartan/amlodipine besilate
[9] Irbesartan/amlodipine besilate
[10] Irbesartan/trichlormethiazide
[11] Olmesartan medoxomil/azelnidipine
[12] Candesartan cilexetil/amlodipine besilate
[13] Candesartan cilexetil/hydrochlorothiazide
[14] Telmisartan/amlodipine besilate
[15] Telmisartan/amlodipine besilate/hydrochlorothiazide
[16] Telmisartan/hydrochlorothiazide
[17] Valsartan/amlodipine besilate
[18] Valsartan/cilnidipine
[19] Valsartan/hydrochlorothiazide
[20] Losartan potassium/hydrochlorothiazide
·Direct renin inhibitor
[1] Aliskiren fumarate

Brand name (name of company)	•Angiotensin-converting enzyme inhibitors [1] Cetapril Tablets 25 mg, and the others (Sumitomo Pharma Co., Ltd., and the others) [2] Tanatril Tablets 2.5, 5, 10, and the others (Mitsubishi Tanabe Pharma Corporation, and the others) [3] Renivace Tablets 2.5, 5, 10, and the others (Organon K.K., and the others) [4] Captoril Tablets 12.5 mg, 25 mg, Captoril Fine Granules 5%, Captoril-R Capsules 18.75 mg, and the others (Alfresa Pharma Corporation, and the others) [5] Acecol Tablets 1 mg, 2 mg, 4 mg, and the others (Alfresa Pharma Corporation, and the others) [6] Adecut 7.5 mg, 15 mg, 30 mg Tablets (Teva Takeda Pharma Ltd.) [7] Odric Tablets 0.5 mg, 1 mg, and the others (Nippon Shinyaku Co., Ltd., and the others) [8] Cibacen Tablets 2.5 mg, 5 mg, 10 mg, and the others (Sun Pharma Japan Limited., and the others) [9] Coversyl Tablets 2 mg, 4 mg, and the others (Kyowa Kirin Co., Ltd., and the others) [10] Zestril Tablets 5, 10, 20, and the others (AstraZeneca K.K., and the others) [10] Longes Tablets 5 mg, 10 mg, 20 mg, and the others (Kyowa Pharmaceutical Industry Co., Ltd., and the others) •Preparations containing angiotensin II receptor blocker [1] Azilva Tablets 10 mg, 20 mg, 40 mg, Azilva Granules 1%, and the others (Takeda Pharmaceutical Company Limited., and the others) [2] Avapro Tablets 50 mg, 100 mg, 200 mg, and the others (Sumitomo Pharma Co., Ltd., and the others) [2] Irbetan Tablets 50 mg, 100 mg, 200 mg, and the others (Shionogi Pharma Co., Ltd., and the others) [3] Olmetec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg, and the others (Daiichi Sankyo Co., Ltd., and the others) [4] Blopress Tablets 2, 4, 8, 12, and the others (Teva Takeda Pharma Ltd., and the others) [5] Micardis Tablets 20 mg, 40 mg, 80 mg, and the others (Boehringer Ingelheim Japan, Inc., and the others) [6] Diovan OD Tablets 20 mg, 40 mg, 80 mg, 160 mg, Diovan Tablets 20 mg, 40 mg, 80 mg, 160 mg, and the others (Novartis Pharma K.K., and the others) [7] Nu-Lotan Tablets 25 mg, 50 mg, 100 mg, and the others (Organon K.K., and the others) [8] Zacras Combination Tablets LD, HD, and the others (Takeda Pharmaceutical Company Limited., and the others) [9] Aimix Combination Tablets LD, HD, and the others (Sumitomo Pharma Co., Ltd., and the others) [10] Irtra Combination Tablets LD, HD (Shionogi Pharma Co., Ltd.) [11] Rezaltas Combination Tablets LD, HD (Daiichi Sankyo Co., Ltd.) [12] Unisia Combination Tablets LD, HD, and the others (Teva Takeda Pharma Ltd., and the others) [13] Ecard Combination Tablets LD, HD, and the others (Teva Takeda Pharma Ltd., and the others)

	[14] Micamlo Combination Tablets AP, BP, and the others (Boehringer Ingelheim Japan, Inc., and the others) [15] Micatrio Combination Tablets (Boehringer Ingelheim Japan, Inc.) [16] Micombi Combination Tablets AP, BP, and the others (Boehringer Ingelheim Japan, Inc., and the others) [17] Exforge Combination OD Tablets, Exforge Combination Tablets, and the others (Novartis Pharma K.K., and the others) [18] Atedio Combination Tablets (EA Pharma Co., Ltd.) [19] Co-Dio Combination Tablets MD, EX, and the others (Novartis Pharma K.K., and the others) [20] Preminent Tablets LD, HD, and the others (Organon K.K., and the others) •Direct renin inhibitor [1] Rasilez Tablets 150 mg (OrphanPacific, Inc.)
Therapeutic category	Antihypertensives, vasodilators
Indications	Hypertension, etc. (Descriptions are omitted because there are many relevant drug products.)

PRECAUTIONS (Revised language is underlined.)

[Under old instructions]

Use in Pregnant, Parturient and Nursing Women (newly added)

Women of child-bearing potential should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc. If administration is considered necessary, attention should be paid to the following points.

(1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.

(2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary.

- This drug can cause foetal and neonatal harm when administered to a pregnant woman.
- If pregnancy is detected or suspected, the attending physician should be consulted immediately.
- If pregnancy is planned, the attending physician should be consulted.

[Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that they were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and kidney, death, etc.) were observed.]

[Under new instructions]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS (newly added)

9.4 Patients with Reproductive Potential

Women of child-bearing potential

Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that the women were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and

kidney, death, etc.) were observed.
Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc., and this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. If administration is considered necessary, attention should be paid to the following points.
(1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.
(2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary.

- This drug can cause foetal and neonatal harm when used to a pregnant woman.
- If pregnancy is detected or suspected, the attending physician should be consulted immediately.
- If pregnancy is planned, the attending physician should be consulted.

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports
Cases involving adverse reactions in foetuses and neonates due to exposure during pregnancy:
•Angiotensin-converting enzyme inhibitors
1(No patient mortalities)
[1] Alacepril
No cases have been reported to date.
[2] Imidapril hydrochloride
No cases have been reported to date.
[3] Enalapril maleate
1 (No patient mortalities)
[4] Captopril
No cases have been reported to date.
[5] Temocapril hydrochloride
No cases have been reported to date.
[6]Delapril hydrochloride
No cases have been reported to date.
[7] Trandolapril
No cases have been reported to date.
[8] Benazepril hydrochloride
No cases have been reported to date.
[9] Perindopril erbumine
No cases have been reported to date.
[10] Lisinopril hydrate
No cases have been reported to date.
•Preparations containing angiotensin II receptor blocker
23 (including 7 fatal cases)
[1] Azilsartan
1(No patient mortalities)
[2] Irbesartan
No cases have been reported to date.
[3] Olmesartan medoxomil

6 (including 4 fatal cases)
[4] Candesartan cilexetil
6 (including 2 fatal cases)
[5] Telmisartan
2 (No patient mortalities)
[6] Valsartan
3 (No patient mortalities)
[7] Losartan potassium
3 (No patient mortalities)
[8] Azilsartan/amlodipine besilate
No cases have been reported to date.
[9] Irbesartan/amlodipine besilate
No cases have been reported to date.
[10] Irbesartan/trichlormethiazide
No cases have been reported to date.
[11] Olmesartan medoxomil/azelnidipine
1 (No patient mortalities)
[12] Candesartan cilexetil/amlodipine besilate
No cases have been reported to date.
[13] Candesartan cilexetil/hydrochlorothiazide
No cases have been reported to date.
[14] Telmisartan/amlodipine besilate
No cases have been reported to date.
[15] Telmisartan/amlodipine besilate/hydrochlorothiazide
No cases have been reported to date.
[16] Telmisartan/hydrochlorothiazide
No cases have been reported to date.
[17] Valsartan/amlodipine besilate
1 (1 fatal case)
[18] Valsartan/cilnidipine
No cases have been reported to date.
[19] Valsartan/hydrochlorothiazide
1 (No patient mortalities)
[20] Losartan potassium/hydrochlorothiazide
No cases have been reported to date.
•Direct renin inhibitor
[1] Aliskiren fumarate
No cases have been reported to date.
Number of patients using the drugs as estimated by the MAHs during the previous 1-year period: Descriptions are omitted because there are many relevant drug products.
Japanese market launch: Descriptions are omitted because there are many relevant drug products.

[Case Summary]
Case summaries can be found in the 1. Revision of Precautions for Drugs Inhibiting the Renin-angiotensin System (page 9 to 12 in this volume of PMDSI).

2 Angiotensin receptor-neprilysin inhibitor
[1] Sacubitril valsartan sodium hydrate

Brand name (name of company)	•Angiotensin receptor-neprilysin inhibitor [1] Entresto Tablets 50 mg, 100 mg, 200 mg (Novartis Pharma K.K.)
Therapeutic category	Antihypertensives, other cardiovascular agents
Indications	<Tablets 50 mg, 100 mg, 200 mg> Chronic cardiac failure The use is limited to patients receiving standard treatment of chronic heart failure. <Tablets 100 mg, 200 mg> Hypertension

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.4 Patients with Reproductive Potential

Women of childbearing potential

Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that they were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and kidney, death, etc.) were observed.

Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc., and this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. If administration is necessary, attention should be paid to the following points.

(1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.

(2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary.

- This drug can cause foetal and neonatal harm when administered to a pregnant woman.
- Appropriate contraceptive methods should be used for a certain period during and after the administration of this drug.
- If pregnancy is detected or suspected, the attending physician should be consulted immediately.
- If pregnancy is planned, the attending physician should be consulted.

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports

• Angiotensin receptor-neprilysin inhibitor

[1] Sacubitril valsartan sodium hydrate

No cases have been reported to date.

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Descriptions are omitted because there are many relevant drug products.

Japanese market launch: Descriptions are omitted because there are many relevant drug products.

3 Mesalazine

Brand name (name of company)	[1] Lialda Tablets 1200 mg (Mochida Pharmaceuticals Co. Ltd.) [2] Asacol tablets 400 mg (Zeria Pharmaceutical Co., Ltd.) [3] Pentasa Tablets 250 mg, 500 mg, Pentasa Granules 94%, Pentasa Suppositories 1 g, Pentasa Enema 1 g (Kyorin Pharmaceutical Co., Ltd.) and the others
Therapeutic category	Other agents affecting digestive organs
Indications	[1] Lialda Tablets 1200 mg, [2] Asacol tablets 400 mg, [3] Pentasa Suppositories 1 g, Pentasa Enema 1 g: Ulcerative colitis (excluding severe cases) [3] Pentasa Tablets 250 mg, 500 mg, Pentasa Granules 94%: Ulcerative colitis (excluding severe cases), Crohn's disease

PRECAUTIONS (Revised language is underlined.)

[Under old instructions]

Adverse Reactions
Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome):

Clinically Significant Adverse Reactions (newly added)
Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson 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.
Drug-induced hypersensitivity syndrome:
Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, hepatic impairment, etc. that may occur even after discontinuation of administration.

[Under new instructions]

11. ADVERSE REACTIONS
Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome)
Drug-induced hypersensitivity syndrome

11.1 Clinically Significant Adverse Reactions (newly added)
Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, hepatic impairment, etc. that may occur even after discontinuation of administration.

Reference information
Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports
Cases involving toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), drug-

induced hypersensitivity syndrome : 10 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period:
[1] Approximately 42 000
[2] Approximately 40 200
[3] Approximately 198 477
Japanese market launch:
[1] Lialda Tablets 1200 mg: November 2016
[2] Asacol tablets 400 mg: December 2009
[3] Pentasa Tablets 250 mg: July 1996, 500 mg: October 2008, Pentasa Granules 94%: December 2015, Pentasa Suppositories 1 g: June 2013, Pentasa Enema 1 g: June 2003

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Male 40s	Ulcerative colitis (none)	1 500 mg 1 day	**Exfoliative dermatitis** 2 months before administration: The patient was diagnosed with ulcerative colitis at a nearby hospital, and started to take salazosulfapyridine (hereinafter referred to as SASP) orally. Pyrexia and skin eruptions occurred. Liver disorder was indicated, and SASP was discontinued. Erythema was observed on the trunk, extremities, and face. He received inpatient care at this hospital. Skin eruptions clearly improved with the prescription by a dermatologist. Day 1 of administration: For the treatment of ulcerative colitis, the patient took 2 tablets of mesalazine 250 mg three times a day for one day. Skin eruptions newly occurred on the trunk, and pyrexia was noted in the morning on the same day. 1 day after administration (Day of discontinuation): Administration of mesalazine was discontinued. 1 day after discontinuation: A biochemical test revealed renal disorder. 2 days after discontinuation: Erythema and pigmentation continued. 6 days after discontinuation: A flare-up of erythema was noted. 7 days after discontinuation: Renal disorder was aggravated, but subsequently it was gradually resolving. On the other hand, skin eruptions persisted. 13 days after discontinuation: Multiple millet seed-sized erythemas accompanied by infiltration occurred. 20 days after discontinuation: Erythema of the trunk tended to improve, and multiple erythemas accompanied by half rice-grain sized infiltration developed in the extremities. 22 days after discontinuation: Desquamation occurred from all the skin eruptions. 31 days after discontinuation: Renal disorder was resolving. Skin eruptions had occurred on the day of administration. Desquamation was noted on the trunk, but the redness continued in the extremities. 32 days after discontinuation: Infiltration of the skin eruptions showed the formation of scabs. 42 days after discontinuation: At the initial visit to Hospital T (during hospitalization at this hospital), generalized erythroderma was noted. At that visit, the patient had already developed sepsis. Eosinophile count markedly increased, and renal impairment, etc. were noted. Under the diagnosis of drug-induced hypersensitivity syndrome (hereinafter referred to as DIHS), antibiotics were used, but they were ineffective. The sepsis tended to be resolving temporarily, and erythroderma also tended to be resolving. However, soon after that, new sepsis (especially relatively weak bacterial infections such as methicillin-susceptible *Staphylocossus aureus* (MSSA) and *Candida*) repeated. A drug-induced lymphocyte stimulation test (hereinafter

					referred to as DLST) was negative for SASP and positive for mesalazine.
				43 days after discontinuation	The patient was transferred to Hospital T. Hydrocortisone cream and heparinoid ointment were prescribed by a dermatologist between the initial visit (before administration of mesalazine) and the last visit (43 days after discontinuation).
				3 months after discontinuation	Skin eruptions tended to be resolving, and administration of prednisolone (hereinafter referred to as PSL) was temporarily discontinued. However, marked thrombocytopenia was noted, and in response to this, administration of PSL was resumed with an increased dose. Within less than a week thereafter, sepsis occurred due to multidrug resistant *Psudomonas aeruginosa* or MRSA, and the skin eruptions were markedly aggravated each time (when pyrexia occurred or general condition was aggravated). High dose γ-globulin therapy and plasma exchange therapy were also performed.
				9 months after discontinuation	Since 9 months after discontinuation of administration, the patient tended not to have sepsis, and he was discharged from the hospital at the end of the same month. He continued oral PSL, systemic topical steroids, home treatment, and oral antifungals on an outpatient basis. After that, he developed hair loss, followed by alopecia universalis, diabetes mellitus, and adrenal cortical insufficiency, etc. These are also considered to be possibly due to immune modulation caused by DIHS. In addition, he had concurrent pustular psoriasis 4 months after the discharge and sepsis 8 months after, which required admission to the hospital again. Each time, the skin eruptions were aggravated to the condition of erythroderma. At this point, the skin eruptions were still exacerbated due to mild common cold, etc., and the dose of PSL could not be reduced. His renal function and endocrine were not stabilized, and he was examined by both the department of internal medicine and dermatology.
				25 months after discontinuation	The patient recovered from exfoliative dermatitis with sequelae.
	Concomitant drugs: None				

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
2	Male 20s	Ulcerative colitis (none)	Unknown 23 Days (Duration of readministration unknown)	**Drug eruption with eosinophilia and general symptom** Day 1 of administration: The patient was diagnosed with ulcerative colitis at a nearby hospital, and mesalazine was administered. Day 24 of administration (day of discontinuation): The patient was referred to this hospital. Since his bloody stool did not improve, administration of mesalazine was changed to SASP. 14 days after discontinuation: Low grade fever and pharyngitis were noted, and the patient took over-the-counter cold drugs. 17 days after discontinuation (Day 1 of readministration: Elevated hepatobiliary enzyme levels and erythema accompanied by generalized itching were observed. These were considered to be drug eruption and hepatic function disorder caused by SASP, and SASP was changed to mesalazine. Day 10 of readministration: Pyrexia, exacerbation of skin eruptions, swollen cervical lymph nodes, elevated hepatobiliary enzyme levels, and appearance of atypical lymphocytes were observed. Therefore, the patient was admitted to the hospital. DIHS was suspected, and all the oral drugs were discontinued. Day 11 of readministration: PSL 40mg/day was administered. The symptoms were resolving temporarily. Day 18 of readministration: Pyrexia, elevated hepatobiliary enzyme levels were noted again, and steroid pulse therapy was performed with an initial dose of PSL 60 mg/day, and it was tapered. Day 77 of readministration: During oral administration of PSL 2.5 mg/day, re-elevation of hepatobiliary enzyme levels was observed, and the steroid pulse therapy was performed again. Date unknown: The dose was being tapered from PSL 60 mg/day, and no flare-ups were observed. Pyrexia and skin eruptions, both of which often occur at the time of flare-ups, were not observed. During the clinical course, reactivation of human herpesvirus 6 (HHV-6) was observed, and the patient was diagnosed with DIHS. A DLST was positive for this drug and negative for SASP and cold drugs.
	Concomitant drugs: Salazosulfapyridine, cold drugs Abstract for the Joint Regional Meeting of the 43rd Regular Meeting of Koshinetsu Regional Branch of the Japanese Society of Gastroenterology and the 65th Meeting of Koshinetsu Regional Branch of Japan Gastroenterological Endoscopy Society (November 15, 16, 2008) 46 (Sho-25)			

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
3	Male 40s	Ulcerative colitis (none)	4 800 mg for 33 days ↓ Discontinuation	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome)**	
				5 days before administration	The patient was admitted to the hospital for remission induction in ulcerative colitis.
				1 days before administration	Remission induction was initiated by intravenous infusion of PSL 70 mg/day (1 mg/kg/day)
				Day 1 of administration	Administration of mesalazine 4 800 mg once a day was initiated for the treatment of ulcerative colitis. Oral treatment with sulfamethoxazole/trimethoprim for prophylaxis of pneumocystis pneumonia due to immunosuppression associated with high dose of PSL, as well as oral treatment with rabeprazole 10 mg/day to prevent gastrointestinal mucosal disorder, was initiated. The symptoms of ulcerative colitis improved in approximately 12 days, and the dose of PSL was tapered by 10 mg every week.
				Day 28 of administration	Remission of the symptoms of ulcerative colitis was achieved without any problems, and the patient was discharged from the hospital. The dose of PSL was gradually reduced to 40 mg/day.
				Day 29 of administration:	The dose of PSL was tapered to 30 mg/day. The patient had a foreign body sensation in his eyes, swelling of eyelid, multiple stomatitis, and swelling face.
				Day 31 of administration	The patient was examined as an outpatient. He was prescribed a topical drug and was instructed to be followed up. However, the symptoms did not improve, and they were exacerbated.
				Day 33 of administration (day of discontinuation)	Rash appeared on the back of both hands, and the patient visited the hospital again. He was urgently admitted to the hospital due to suspected oculomucocutaneous syndrome (Stevens-Johnson syndrome). Body temperature was 36.4°C. Swelling of eyelid, bulbar conjunctival hyperaemia, redness of face/swelling face, watery nasal discharge, stomatitis, anal pain, and erythematous swelling of back of both hands were observed. DLST: Strongly positive for mesalazine, negative for sulfamethoxazole/ trimethoprim and rabeprazole He was diagnosed with oculomucocutaneous syndrome (Stevens-Johnson syndrome) associated with mesalazine. Administration of mesalazine, sulfamethoxazole/trimethoprim, lansoprazole was discontinued. Systemic steroid treatments, injection of immunoglobulin, and topical steroids to the eyes were initiated. Removal of pseudomembranes was initiated. Sulfamethoxazole/trimethoprim and rabeprazole were changed to atovaquone and famotidine before the results of DLST were obtained.
				1 day after discontinuation	PSL 65 mg/day was administered.
				4 days after discontinuation	Administration of injection of immunoglobulin was terminated.

					Exacerbation of symptoms continued after the start of treatment. Erythema, formation of blistering, and abrasion, which were extensively distributed over the entire body including palms and soles, were observed. Mucosal lesions were observed in lip/oral mucosa junctions and anal mucosa. Also, methylprednisolone 500 mg/day was administered by intravenous infusion for 3 days since increased eye pain, corneal opacity, and formation of pseudomembranes were observed.
				7 days after discontinuation	The symptoms started to improve. The dose of PSL was tapered from 70 mg/day.
				21 days after discontinuation	Administration of immunomodulatory agent was initiated for ulcerative colitis.
				23 days after discontinuation	Removal of pseudomembranes was completed.
				24 days after discontinuation	Skin/mucosal lesions tended to heal. Some nails deformed and fell off; however they recovered later. The patient was discharged from the hospital.
					Ocular lesions left him with visual impairment due to opacity in the corneal parenchyma as a sequela.
	Concomitant drugs: Acetaminophen, rabeprazole sodium, sulfamethoxazole/trimethoprim, prednisolone				

4 Zinc acetate hydrate

Brand name (name of company)	Nobelzin Tablets 25 mg, 50 mg, Nobelzin Granules 5% (Nobelpharma Co., Ltd.), and the others
Therapeutic category	Antidotes
Indications	•Wilson's disease (hepato-lenticular degeneration) •Hypozincaemia

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

11. ADVERSE REACTIONS	Gastric ulcer Gastric ulcer with haemorrhage may occur.
11.1 Clinically Significant Adverse Reactions (newly added)	
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving peptic ulcer: 7 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Wilson’s disease: Approximately 250 Hypozincaemia: Approximately 98 000 Japanese market launch: Tablets 25 mg, 50 mg: February 2015 Granules 5%: February 2023

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
administration
duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
80s</td><td>Hypozincaemia
(postoperation of lung cancer, hypertension, diabetes mellitus, old myocardial infarction, prostate cancer, chronic renal failure, hyperlipidaemia)</td><td>150 mg
33 days</td><td>Gastric ulcer with haemorrhage
Medical history: Left lung lower lobectomy
Allergic history: None
The patient had no history of gastric ulcer before administration of zinc acetate hydrate or of H. pylori tests.
History of adverse drug reaction: None
Approximately 2 years before administration: The patient was admitted to the hospital for the treatment of lung cancer. He was hospitalized for approximately 3 months including resting cure.
11 days before administration: Lung cancer surgery was performed.
1 day before administration: Retention of food residues was noted, and gastrointestinal obstruction was suspected. Therefore, an upper gastrointestinal tract endoscopy was performed, revealing no gastric mucosal lesion.
Day 1 of administration: Administration of zinc acetate hydrate 50 mg×3 times/day was initiated.
26 days after administration: Gastric ulcer with haemorrhage occurred. The patient vomited blood. Gastric ulcer was identified by an endoscopy. He received treatments including omeprazole sodium injection. He was fasted and received a gastric secretion inhibitor for the treatment of gastric ulcer with haemorrhage.
27 days after administration: An endoscopy was performed again, revealing multiple gastric ulcers (3 ulcers on the posterior wall of the upper body)
32 days after administration (day of discontinuation): Administration of zinc acetate hydrate was discontinued.
42 days after discontinuation: The patient recovered from gastric ulcer with haemorrhage. He was discharged from the hospital.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table>
<tr><th></th><th>Before administration of zinc acetate hydrate</th><th>18 days after administration</th><th>27 days after administration (1 day after onset)</th><th>41 days after discontinuation</th></tr>
<tr><td>RBC</td><td>-</td><td>2.94×10^6</td><td>2.36×10^6</td><td>3.51×10^6</td></tr>
<tr><td>Haemoglobin (g/dL)</td><td>-</td><td>8.6</td><td>7.3</td><td>10.8</td></tr>
<tr><td>Haematocrit (%)</td><td>-</td><td>28.0</td><td>22.3</td><td>33.8</td></tr>
<tr><td>Platelet count</td><td>-</td><td>421×10^3</td><td>233×10^3</td><td>326×10^3</td></tr>
<tr><td>MCV (fL)</td><td>-</td><td>95.4</td><td>94.3</td><td>96.3</td></tr>
<tr><td>MCH (pg)</td><td>-</td><td>29.4</td><td>30.7</td><td>30.9</td></tr>
<tr><td>MCHC (g/dL)</td><td>-</td><td>30.8</td><td>32.6</td><td>32.1</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant drugs: Aspirin, prasugrel hydrochloride, acotiamide hydrochloride hydrate, rosuvastatin calcium, rikkunshito extract, telmisartan/amlodipine besilate</td></tr>
</table>

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/ age</th><th>Reason for use (complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>2</td><td>Male
60s</td><td>Hypozincaemia (acute pyelonephritis, primary central nervous system diffuse B-cell lymphoma, depressed state, schizophrenia, insomnia, inappetence)</td><td>150 mg
7 days</td><td>Gastric ulcer with haemorrhage
Allergic history: None
History of adverse drug reaction: None
Before administration of zinc acetate hydrate: No endoscopy had been performed before. The patient had no gastrointestinal symptoms or no history of gastric ulcer.
4 months before administration: Radiation therapy was performed (site: Brain).
1 day before administration: The patient was admitted to the hospital due to acute pyelonephritis. He was hospitalized for 2 weeks including resting cure.
Day 1 of administration: Administration of zinc acetate hydrate 50 mg×3 times/day was initiated.
2 days after administration: Gastric ulcer with haemorrhage occurred. The patient vomited blood. An upper gastrointestinal tract endoscopy revealed blood pooling and multiple ulcers in the stomach. However, endoscopic haemostasis was not performed since no active bleeding from gastric ulcers was found. He was fasted and received a proton pump inhibitor for the treatment of gastric ulcer with haemorrhage.
4 days after administration: Multiple ulcers and erosion accompanied by mucosa redness and white film were identified by an upper gastrointestinal tract endoscopy. Small erosion with atypical regenerative epithelium was confirmed by endoscopic biopsy.
6 days after administration (day of discontinuation): Blood H. pylori antibody was negative.
7 days after discontinuation: The patient recovered from gastric ulcer with haemorrhage. He was discharged from the hospital.
6 weeks after discontinuation: Multiple ulcer scars in the stomach were observed by an upper gastrointestinal tract endoscopy. Active ulcers, erosion, mucosa redness, and white film had disappeared.</td></tr>
<tr><td colspan="4">Laboratory test value
<table>
<tr><th></th><th>1 day before administration</th><th>2 days after administration (Day of onset)</th><th>5 days after administration</th></tr>
<tr><td>RBC</td><td>3.20×10^6</td><td>3.07×10^6</td><td>3.21×10^6</td></tr>
<tr><td>Haemoglobin (g/dL)</td><td>10.9</td><td>10.4</td><td>10.6</td></tr>
<tr><td>Haematocrit (%)</td><td>30.4</td><td>29.6</td><td>32.5</td></tr>
<tr><td>Platelet count</td><td>29×10^3</td><td>59×10^3</td><td>224×10^3</td></tr>
<tr><td>MCV (fL)</td><td>95.0</td><td>96.4</td><td>101.4</td></tr>
<tr><td>MCH (pg)</td><td>34.1</td><td>33.9</td><td>33.1</td></tr>
<tr><td>MCHC (g/dL)</td><td>35.9</td><td>35.1</td><td>32.7</td></tr>
</table></td></tr>
<tr><td colspan="4">Concomitant drugs: Trazodone hydrochloride, risperidone, suvorexant, acetaminophen, meropenem hydrate</td></tr>
</table>

4
Revision of Precautions (No.341)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated May 9, 2023.

1 Antihypertensives, vasodilators

[1] Azilsartan
[2] Azilsartan/amlodipine besilate
[3] Alacepril
[4] Aliskiren fumarate
[5] Imidapril hydrochloride
[6] Irbesartan
[7] Irbesartan/amlodipine besilate
[8] Irbesartan/trichlormethiazide
[9] Enalapril maleate
[10] Olmesartan medoxomil
[11] Olmesartan medoxomil/azelnidipine
[12] Captopril
[13] Candesartan cilexetil
[14] Candesartan cilexetil/amlodipine besilate
[15] Candesartan cilexetil/hydrochlorothiazide
[16] Temocapril hydrochloride
[17] Delapril hydrochloride
[18] Telmisartan
[19] Telmisartan/amlodipine besilate
[20] Telmisartan/amlodipine besilate/hydrochlorothiazide
[21] Telmisartan/hydrochlorothiazide
[22] Trandolapril
[23] Valsartan
[24] Valsartan/amlodipine besilate
[25] Valsartan/cilnidipine
[26] Valsartan/hydrochlorothiazide
[27] Benazepril hydrochloride
[28] Perindopril erbumine
[29] Lisinopril hydrate
[30] Losartan potassium
[31] Losartan potassium/hydrochlorothiazide

Brand name
[1] Azilva Tablets 10 mg, 20 mg, 40 mg, Azilva Granules 1% (Takeda Pharmaceutical Company Limited.)
[2] Zacras Combination Tablets LD, HD (Takeda Pharmaceutical Company Limited.)

[3] Cetapril Tablets 25 mg (Sumitomo Pharma Co., Ltd.)
[4] Rasilez Tablets 150 mg (OrphanPacific, Inc.)
[5] Tanatril Tablets 2.5, 5, 10 (Mitsubishi Tanabe Pharma Corporation)
[6] Avapro Tablets 50 mg, 100 mg, 200 mg (Sumitomo Pharma Co., Ltd.)
Irbetan Tablets 50 mg, 100 mg, 200 mg (Shionogi Pharma Co., Ltd.)
[7] Aimix Combination Tablets LD, HD (Sumitomo Pharma Co., Ltd.)
[8] Irtra Combination Tablets LD, HD (Shionogi Pharma Co., Ltd.)
[9] Renivace Tablets 2.5, 5, 10 (Organon K.K.)
[10] Olmetec OD Tablets 5 mg, 10 mg, 20 mg, 40 mg (Daiichi Sankyo Co., Ltd.)
[11] Rezaltas Combination Tablets LD, HD (Daiichi Sankyo Co., Ltd.)
[12] Captoril Tablets 12.5 mg, 25 mg, Captoril Fine Granules 5%, Captoril-R Capsules 18.75 mg (Alfresa Pharma Corporation)
[13] Blopress Tablets 2, 4, 8, 12 (Teva Takeda Pharma Ltd.)
[14] Unisia Combination Tablets LD, HD (Teva Takeda Pharma Ltd.)
[15] Ecard Combination Tablets LD, HD (Teva Takeda Pharma Ltd.)
[16] Acecol Tablets 1 mg, 2 mg, 4 mg (Alfresa Pharma Corporation)
[17] Adecut 7.5 mg, 15 mg, 30 mg Tablets (Teva Takeda Pharma Ltd.)
[18] Micardis Tablets 20 mg, 40 mg, 80 mg (Boehringer Ingelheim Japan, Inc.)
[19] Micamlo Combination Tablets AP, BP (Boehringer Ingelheim Japan, Inc.)
[20] Micatrio Combination Tablets (Boehringer Ingelheim Japan, Inc.)
[21] Micombi Combination Tablets AP, BP (Boehringer Ingelheim Japan, Inc.)
[22] Odric Tablets 0.5 mg, 1 mg (Nippon Shinyaku Co., Ltd.)
[23] Diovan OD Tablets 20 mg, 40 mg, 80 mg, 160 mg, Diovan Tablets 20 mg, 40 mg, 80 mg, 160 mg (Novartis Pharma K.K.)
[24] Exforge Combination OD Tablets, Exforge Combination Tablets (Novartis Pharma K.K.)
[25] Atedio Combination Tablets (EA Pharma Co., Ltd.)
[26] Co-Dio Combination Tablets MD, EX (Novartis Pharma K.K.)
[27] Cibacen Tablets 2.5 mg, 5 mg, 10 mg (Sun Pharma Japan Limited.)
[28] Coversyl Tablets 2 mg, 4 mg (Kyowa Kirin Co., Ltd.)
[29] Zestril Tablets 5, 10, 20 (AstraZeneca K.K.)
Longes Tablets 5 mg, 10 mg, 20 mg (Kyowa Pharmaceutical Industry Co., Ltd.)
[30] Nu-Lotan Tablets 25 mg, 50 mg, 100 mg (Organon K.K.)
[31] Preminent Tablets LD, HD (Organon K.K.)

[Under old instructions]

Use in Pregnant, Parturient and Nursing Women (newly added)

Women of child-bearing potential should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc. If administration is considered necessary, attention should be paid to the following points.
(1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.
(2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be

	provided during administration when necessary. • This drug can cause foetal and neonatal harm when administered to a pregnant woman. • If pregnancy is detected or suspected, the attending physician should be consulted immediately. • If pregnancy is planned, the attending physician should be consulted. [Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that they were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and kidney, death, etc.) were observed.]
[Under new instructions] **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS (newly added)**	9.4 Patients with Reproductive Potential Women of child-bearing potential Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that the women were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and kidney, death, etc.) were observed. Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc., and this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. If administration is considered necessary, attention should be paid to the following points. (1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately. (2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary. • This drug can cause foetal and neonatal harm when used to a pregnant woman. • If pregnancy is detected or suspected, the attending physician should be consulted immediately. • If pregnancy is detected or suspected, the attending physician should be consulted immediately.

2 Antihypertensives, other cardiovascular agents

Sacubitril valsartan sodium hydrate

Brand name	Entresto Tablets 50 mg, 100 mg, 200 mg (Novartis Pharma K.K.)
[Under new instructions] **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS** **9.4 Patients with Reproductive Potential**	Women of childbearing potential Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that they were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and kidney, death, etc.) were observed. Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc., and this drug should be administered only if

the potential therapeutic benefits are considered to outweigh the potential risks. If administration is necessary, attention should be paid to the following points.
(1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.
(2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary.

- This drug can cause foetal and neonatal harm when administered to a pregnant woman.
- Appropriate contraceptive methods should be used for a certain period during and after the administration of this drug.
- If pregnancy is detected or suspected, the attending physician should be consulted immediately.
- If pregnancy is planned, the attending physician should be consulted.

3 Other agents affecting digestive organs

Mesalazine

Brand name

[1] Lialda Tablets 1200 mg (Mochida Pharmaceuticals Co. Ltd.)
[2] Asacol tablets 400 mg (Zeria Pharmaceutical Co., Ltd.)
[3] Pentasa Tablets 250 mg, 500 mg, Pentasa Granules 94%, Pentasa Suppositories 1 g, Pentasa Enema 1 g (Kyorin Pharmaceutical Co., Ltd.)
and the others

[Under old instructions]

Adverse Reactions
Clinically Significant Adverse Reactions (newly added)

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome):
Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson 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.
Drug-induced hypersensitivity syndrome:
Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, hepatic impairment, etc. that may occur even after discontinuation of administration.

[Under new instructions]

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

Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome)
Drug-induced hypersensitivity syndrome
Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash,

	pyrexia, hepatic impairment, etc. that may occur even after discontinuation of administration.

4 Antidotes

Zinc acetate hydrate

Brand name	Nobelzin Tablets 25 mg, 50 mg, Nobelzin Granules 5% (Nobelpharma Co., Ltd.), and the others
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Gastric ulcer Gastric ulcer with haemorrhage may occur.

5 Agents affecting metabolism, n.e.c. (not elsewhere classified)

Leflunomide

Brand name	Arava Tablets 10 mg, 20 mg, 100 mg (Sanofi K.K.)
[Under old instructions]	
Important Precautions	Administration of this drug should be discontinued if serious adverse reactions, such as pancytopenia, oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, skin ulcer, serious infection, or serious liver disorder occur. A drug elimination procedure should be preferably performed.
Adverse Reactions	Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, skin ulcer:
Clinically Significant Adverse Reactions	Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis or skin ulcer may occur. If these symptoms occur, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS	Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis, skin ulcer
11.1 Clinically Significant Adverse Reactions	Administration of this drug should be discontinued. A drug elimination procedure should be preferably performed.

6 Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria

[1] Ampicillin hydrate
[2] Ampicillin sodium

Brand name	[1] Viccillin Capsules 250 mg, Viccillin Dry Syrup 10% (Meiji Seika Pharma Co., Ltd.) [2] Viccillin For Injection 0.25 g, 0.5 g, 1 g, 2 g (Meiji Seika Pharma Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Hepatic impairment may occur. Periodic tests should be performed.
11. ADVERSE REACTIONS	Hepatic impairment Hepatic impairment accompanied by increased levels of AST and ALT, etc. may occur.

11.1 Clinically Significant Adverse Reactions (newly added)	

7 Other antibiotic preparations

[1] Ampicillin hydrate/cloxacillin sodium hydrate
[2] Ampicillin sodium/cloxacillin sodium hydrate

Brand name	[1] Viccillin-S Combination Tablets (Meiji Seika Pharma Co., Ltd.) [2] Viccillin-S100 For Injection, Viccillin-S500 For Injection, Viccillin-S1000 For Injection (Meiji Seika Pharma Co., Ltd.)
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Hepatic impairment accompanied by increased levels of AST and ALT, etc. may occur. Patients should be carefully monitored through methods such as periodic tests. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Hepatic impairment may occur. Periodic tests should be performed.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Hepatic impairment Hepatic impairment accompanied by increased levels of AST and ALT, etc. may occur.

8 X-ray contrast agents

Ioversol

Brand name	Optiray 240 Injection Syringe 100 mL, and the others, Optiray 320 Injection 20 mL, and the others (Guerbet Japan KK)
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions	Skin disorders: Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and appropriate measures should be taken if symptoms such as pyrexia, erythema, small pustules, pruritus, ocular hyperaemia, or stomatitis are observed.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Skin disorders Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and appropriate measures should be taken if symptoms such as pyrexia, erythema, small pustules, pruritus, ocular hyperaemia, or stomatitis are observed.

5

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of March 31, 2023)
◎: Products for which EPPV was initiated after March 1, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Cemiplimab (genetical recombination) Libtayo I.V. Infusion 350 mg	Sanofi K.K.	March 30, 2023
◎	Tremelimumab (genetical recombination) Imjudo Injection 25 mg, 300 mg	AstraZeneca K.K.	March 15, 2023
◎	Ferric derisomaltose MonoVer for I.V. Injection 500 mg, 1000 mg	Nippon Shinyaku Co., Ltd.	March 15, 2023
◎	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) *1 Comirnaty intramuscular injection for 5 to 11 years old (Bivalent: Original/Omicron BA.4-5)	Pfizer Japan Inc.	March 3, 2023
	Dexmedetomidine hydrochloride*2 Precedex Injections Solution 200 μg [Pfizer], 200 μg/50 mL syringe [Pfizer]	Pfizer Japan Inc.	February 24, 2023
	Risankizumab (genetical recombination)*3 Skyrizi Auto dosers 360 mg	AbbVie GK	February 13, 2023
	Meningococcal polysaccharide-tetanus toxoid conjugate (serogroups A, C, W, and Y) MenQuadfi intramuscular injection	Sanofi K.K.	February 10, 2023
	Abaloparatide acetate Ostabalo Subcutaneous Injection Cart 1.5 mg	Teijin Pharma Limited.	January 30, 2023
	Risankizumab (genetical recombination) Skyrizi Intravenous infusion 600 mg	AbbVie GK	January 13, 2023
	Caplacizumab (genetical recombination) Cablivi Injection 10 mg	Sanofi K.K.	December 23, 2022
	Valemetostat tosilate Ezharmia Tablets 50 mg, 100 mg	Daiichi Sankyo Co., Ltd.	December 20, 2022
	Ozoralizumab (genetical recombination) Nanozora 30 mg Syringes for S.C. Injection	Taisho Pharmaceutical Co., Ltd.	December 1, 2022

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Spikevax Intramuscular Injection (Bivalent: Original/Omicron BA.4-5)	Moderna Japan Co., Ltd.	November 28, 2022
	Ensitrelvir fumaric acid Xocova Tablets 125 mg	Shionogi & Co., Ltd.	November 24, 2022
	Human C1-inactivator Berinert S.C. Injection 2000	CSL Behring K.K.	November 21, 2022
	Vutrisiran sodium Amvuttra Subcutaneous Injection 25 mg Syringe	Alnylam Japan K.K.	November 18, 2022
	Deucravacitinib Sotyktu tablets 6 mg	Bristol-Myers Squibb K.K.	November 16, 2022
	Tezepelumab (genetical recombination) Tezspire Subcutaneous Injection 210 mg	AstraZeneca K.K.	November 16, 2022
	Spesolimab (genetical recombination) Spevigo 450 mg for I.V. Infusion	Nippon Boehringer Ingelheim Co., Ltd.	November 16, 2022
	Fenfluramine hydrochloride Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	November 16, 2022
	Selumetinib sulfate Koselugo Capsules 10 mg, 25 mg	Alexion Pharma Godo Kaisha	November 16, 2022
	Rivaroxaban*4 Xarelto tablets 2.5 mg	Bayer Yakuhin Ltd.	October 24, 2022
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	October 19, 2022

*1 Prevention of infectious disease caused by SARS-CoV-2

*2 Sedation of non-intubated pediatric patients in non-invasive procedures and examinations

*3 Maintenance therapy for moderately to severely active Crohn's disease (only for patients who have not adequately responded to conventional treatments)

*4 Prevention of thrombus/embolus formation in patients with peripheral arterial disease after lower extremity revascularization