Pharmaceuticals and Medical Devices Safety Information

No. 371 March 2020

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Available information is listed here.

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Pharmaceuticals and Medical Devices Safety Information

No. 371 March 2020

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

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

If providers of medical care and pharmaceutical products such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse Drug Reaction
ALT	Alanine aminotransferease
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PT-INR	Prothrombin time international normalized ratio

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For the Promotion of Pediatric Clinical Development (development and safety measures) through Active Use of Medical Information Database (Part 2)

Assessment of Adverse Events with Use of the Pediatric Medical Data Collecting System and Efforts Focused on Future Utilization of the System

1. Introduction

In the preceding issue (Pharmaceuticals and Medical Devices Safety Information No. 370), the background to the creation and maintenance of a medical information database in pediatric disciplines (Pediatric Medical Data Collecting System; hereinafter referred to as the "System"), summary of the number of accumulated data, and a survey on Drug Use in Children through Active Use of the System were introduced.

This issue outlines the assessment of adverse events related to drug administration with use of the System and future utilization of the System.

2. Actual prescription practices with influenza antiviral drugs and associated adverse events (e.g. abnormal behaviour)

Adverse events (e.g. abnormal behaviour) associated with administration of influenza antiviral drugs are being assessed/analyzed in the current circumstances by research groups, etc. organized for public research. The safety of influenza antiviral drugs have also been described as "Safety of Influenza Antiviral Drugs" in Pharmaceuticals and Medical Devices Safety Information[1)].

Recently, an investigation of actual prescription practices with influenza antiviral drugs and associated adverse events (e.g. abnormal behaviour) was attempted using data accumulated in the System. Some of its results are presented here.

[Investigation method]

1) Data period: April 2016 to March 2017 (1 year)
2) Patient's age: Less than 20 years (age as of the end of March 2017)
3) Data extraction:
   - 3-1) Influenza-related disease names
     - Influenza due to certain identified influenza viruses
     - Influenza due to other identified influenza virus
     - Influenza with pneumonia
     - Influenza with other respiratory manifestations, influenza virus identified
     - Influenza with other manifestations, other influenza virus identified
     - Influenza, virus not identified
     - Influenza with pneumonia, virus not identified
     - Influenza with other respiratory manifestations, virus not identified
     - Influenza with other manifestations, virus not identified
   - 3-2) Influenza antiviral drugs, with their trade name (abbreviated) within parentheses
     - Zanamivir hydrate (Relenza)
     - Oseltamivir phosphate (Tamiflu)
     - Peramivir hydrate (Rapiacta)
     - Laninamivir octanoate hydrate (Inavir)
     - Amantadine hydrochloride (Symmetrel)

       * Baloxavir marboxil (Xofluza) is not included in the investigation because it was not marketed during this data period.
   - 3-3) Complications, with corresponding disease names extracted within parentheses
     - Influenza encephalopathy (influenza encephalopathy)
     - Other types of encephalopathy (encephalopathy, acute encephalopathy, acute encephalopathy with seizures and late reduced diffusion, acute encephalopathy with biphasic seizures and late reduced diffusion)
     - Abnormal behaviour (abnormal behaviour)
     - Delirium (delirium, febrile delirium)

- Disturbed consciousness (disturbed consciousness, transient consciousness disturbance, acute consciousness disturbance, persistent consciousness disturbance)
- Convulsion (convulsion, seizure, seizure with late reduced diffusion)
- Febrile convulsion (heat cramps, febrile convulsion, recurrence of febrile convulsion, simple febrile convulsion, uncomplicated febrile convulsion, febrile seizure with late reduced diffusion, complex febrile convulsion)

Investigation results obtained by the above investigation method are as shown below. With regard to investigation results, as stated in the preceding issue, the investigation of actual prescription practices has its limitations because it is an investigation that uses data of order information (prescription order), not dosing information. It is not possible to accurately confirm the facts that patients actually took the drug and dosages that they actually took, and it cannot track prescriptions beyond existing data because all prescription discontinuation order information has not been collected. Numerical values less than 3 cases are shown as * in conformity with “Guidelines for Utilization of Medical Data, etc. in the Pediatric Medical Data Collecting System (trial utilization period)” (hereinafter the same).

[Investigation results]

2-1. Actual prescription practices with influenza antiviral drugs for the diagnosis of influenza

During the data period of this investigation, the total number of patients with influenza was 21 834, including 10 200 (approximately 50%) with “definitive diagnosis” and 11 634 (approximately 70%) with “suspected diagnosis.” In the definitive diagnosis cases of influenza, type A accounted for 60%, type B for10%, and unknown whether type A or B for 30%. Of the total number of patients (21 834), influenza antiviral drugs were prescribed to 7 042 (32%). Among them, influenza antiviral drugs were prescribed to 6 208 patients (60%) with definitive diagnosis (10 200 patients) and influenza antiviral drugs were prescribed to 834 patients (7%) with suspected diagnosis (11 634 patients).

* During the data period of this investigation, when a disease name of influenza was given (diagnosed with influenza) more than once to one patient, all of the names were included in the count. “Definitive diagnosis” and “suspected diagnosis” were extracted and tabulated from the disease name information described in electronic medical chart information as the information source of the System. These are not necessarily the same as clinical diagnoses. Also, cases for which “prophylaxis” was clearly mentioned in electronic medical chart information were excluded from the tabulation.

Age group	Age		Diagnosed with influenza					Total
			Definitive diagnosis			Suspected diagnosis		
		Influenza antiviral drug prescribed	Influenza antiviral drug not prescribed	Total	Influenza antiviral drug prescribed	Influenza antiviral drug not prescribed	Total	
Newborns/nursing infants	0	95	168	263	13	508	521	784
Toddlers and preschoolers	1	304	319	623	95	1,707	1,802	2,425
	2	420	301	721	96	1,381	1,477	2,198
	3	422	325	747	72	1,057	1,129	1,876
	4	559	345	904	106	1,021	1,127	2,031
	5	608	349	957	86	900	986	1,943
School-age children	6	572	344	916	66	783	849	1,765
	7	529	319	848	53	557	610	1,458
	8	493	313	806	57	509	566	1,372
	9	384	221	605	39	437	476	1,081
	10	401	202	603	33	374	407	1,010
	11	344	170	514	19	331	350	864
	12	288	148	436	34	316	350	786
	13	258	131	389	25	256	281	670
	14	210	148	358	16	236	252	610
15 to < 20 years	15	103	80	183	*	166	168	351
	16	81	29	110	8	93	101	211
	17	79	43	122	9	89	98	220
	18	35	27	62	3	50	53	115
	19	23	10	33	*	29	31	64
Total		6,208	3,992	10,200	834	10,800	11,634	21,834

One of the characteristics of the System is collecting information from pediatric medical institutions and clinics. This enables extraction of actual prescription practices at pediatric medical institutions and clinics respectively. The results show that the prescription rate of influenza antiviral drugs for definitive diagnosis was approximately 30% at pediatric medical institutions and approximately 70% at clinics. The prescription rate of influenza antiviral drugs was substantially higher at clinics than at pediatric medical institutions. However, the System is unable to grasp cases that visited a clinic and were prescribed an influenza antiviral drug, and subsequently visited a pediatric medical institution because the disease became serious, and therefore it is not possible to identify the reason for the low prescription rate of influenza antiviral drugs at pediatric medical institutions.

2-2. Actual prescription practices with influenza antiviral drugs (numbers of prescriptions by age group/trade name)

	Number of prescriptions of influenza antiviral drug							Proportion of prescriptions of influenza antiviral drug						
Age group	Age	Tamiflu DS	Tamiflu CAP	Inavir	Relenza	Rapiacta	Total	Age	Tamiflu DS	Tamiflu CAP	Inavir	Relenza	Rapiacta	Total
Newborns/nursing infants	0	101	0	0	0	*	103	0	98.1%	0.0%	0.0%	0.0%	*	100.0%
Toddlers and preschoolers	1	328	0	0	0	9	337	1	97.3%	0.0%	0.0%	0.0%	2.7%	100.0%
	2	476	*	0	0	5	482	2	98.8%	*	0.0%	0.0%	1.0%	100.0%
	3	458	0	0	0	7	465	3	98.5%	0.0%	0.0%	0.0%	1.5%	100.0%
	4	635	0	8	0	6	649	4	97.8%	0.0%	1.2%	0.0%	0.9%	100.0%
	5	608	0	70	15	10	703	5	86.5%	0.0%	10.0%	2.1%	1.4%	100.0%
	6	491	0	129	31	7	658	6	74.6%	0.0%	19.6%	4.7%	1.1%	100.0%
School-age children	7	273	*	205	113	6	598	7	45.7%	*	34.3%	18.9%	1.0%	100.0%
	8	189	3	215	138	6	551	8	34.3%	0.5%	39.0%	25.0%	1.1%	100.0%
	9	98	3	202	104	5	412	9	23.8%	0.7%	49.0%	25.2%	1.2%	100.0%
	10	43	12	217	147	4	423	10	10.2%	2.8%	51.3%	34.8%	0.9%	100.0%
	11	24	12	189	122	3	350	11	6.9%	3.4%	54.0%	34.9%	0.9%	100.0%
	12	15	12	186	85	3	301	12	5.0%	4.0%	61.8%	28.2%	1.0%	100.0%
	13	5	24	163	78	*	272	13	1.8%	8.8%	59.9%	28.7%	*	100.0%
	14	3	27	136	55	8	229	14	1.3%	11.8%	59.4%	24.0%	3.5%	100.0%
15 to < 20 years	15	3	13	60	33	0	109	15	2.8%	11.9%	55.0%	30.3%	0.0%	100.0%
	16	4	12	49	18	*	84	16	4.8%	14.3%	58.3%	21.4%	*	100.0%
	17	3	6	53	19	0	81	17	3.7%	7.4%	65.4%	23.5%	0.0%	100.0%
	18	*	*	23	10	*	38	18	*	*	60.5%	26.3%	*	100.0%
	19	*	*	16	5	*	25	19	*	*	64.0%	20.0%	*	100.0%
Total		3,759	130	1,921	973	87	6,870	Total	54.7%	1.9%	28.0%	14.2%	1.3%	100.0%

The proportions of prescriptions of influenza antiviral drugs by trade name showed tendencies toward prescriptions of Tamiflu DS to the age groups up to toddlers and preschoolers and prescriptions of Inavir or Relenza as an inhaled drug to the age groups of school-age children and older. Also, at pediatric medical institutions, although the number was small, prescriptions of Rapiacta were identified in all age groups.

2-3. Number of patients with a complication(s) and actual prescription practices with influenza antiviral drugs

(number of prescriptions of influenza antiviral drugs and proportion of prescriptions of influenza antiviral drugs by complication diagnosed in “less than 7 days” after diagnosis of influenza)

Influenza diagnosis classification	Complication category	Number of patients	Number of prescriptions of influenza antiviral drug						Complication category	Proportion of prescriptions of influenza antiviral drug					
			Tamiflu DS	Tamiflu CAP	Inavir	Relenza	Rapiacta	Total		Tamiflu DS	Tamiflu CAP	Inavir	Relenza	Rapiacta	Total
Definitive diagnosis	Influenza encephalopathy (including other types of encephalopathy)	41	7	0	0	*	11	19	Influenza encephalopathy (including other types of encephalopathy)	36.8%	0.0%	0.0%	*	57.9%	100.0%
	Abnormal behaviour	5	0	0	0	0	0	0	Abnormal behaviour	NA	NA	NA	NA	NA	NA
	Delirium	22	*	0	0	0	*	*	Delirium	*	0.0%	0.0%	0.0%	*	100.0%
	Disturbance of consciousness	35	6	0	0	*	6	13	Disturbance of consciousness	46.2%	0.0%	0.0%	*	46.2%	100.0%
	Convulsion	85	31	0	0	0	9	40	Convulsion	77.5%	0.0%	0.0%	0.0%	22.5%	100.0%
	Febrile convulsion	163	40	0	*	*	12	55	Febrile convulsion	72.7%	0.0%	*	*	21.8%	100.0%
Suspected diagnosis	Influenza encephalopathy (including other types of encephalopathy)	50	3	0	0	0	*	4	Influenza encephalopathy (including other types of encephalopathy)	75.0%	0.0%	0.0%	0.0%	*	100.0%
	Abnormal behaviour	0	0	0	0	0	0	0	Abnormal behaviour	NA	NA	NA	NA	NA	NA
	Delirium	10	0	0	0	0	0	0	Delirium	NA	NA	NA	NA	NA	NA
	Disturbance of consciousness	81	3	0	0	0	*	4	Disturbance of consciousness	75.0%	0.0%	0.0%	0.0%	*	100.0%
	Convulsion	186	3	0	0	0	3	6	Convulsion	50.0%	0.0%	0.0%	0.0%	50.0%	100.0%
	Febrile convulsion	289	4	0	0	0	*	5	Febrile convulsion	80.0%	0.0%	0.0%	0.0%	*	100.0%
Total		967	98	0	*	3	45	148	Total	66.2%	0.0%	*	2.0%	30.4%	100.0%

Of patients with influenza encephalopathy (including other types of encephalopathy), complications were observed in 91 patients (including 41 patients with definitive diagnosis of influenza) in less than 7 days after diagnosis of influenza. Also, abnormal behaviour was observed in 5 patients, but for all of the cases, there was no prescription of influenza antiviral drugs in the data.

The data period for this investigation is 1 year, and it is not adequate to assess adverse reactions to influenza antiviral drugs based on these data. In the future, an extension of the data period for the investigation and a more in-depth analysis of data will enable detection of signals of adverse reactions or continuous monitoring of things such as onset time of complications after prescriptions of influenza antiviral drugs.

3. Actual prescription practices with pivoxil-containing antimicrobial drugs and associated adverse events (carnitine deficiency)

Regarding the onset of hypocarnitinaemia due to antimicrobial drugs that contain pivoxil and the onset of hypoglycaemia, convulsion, encephalopathy, etc. associated with hypocarnitinaemia, PMDA provided information on the risks and proper use of these agents in April 2012[2)], and a precautionary statement has been included in sections such as Important Precautions in the package inserts.

Also, in July 2019, the Japan Pediatric Society made a similar precautionary statement[3)].

In this context, an investigation of actual prescription practices with antimicrobial drugs that contain pivoxil and associated adverse events (carnitine deficiency) was conducted using the System. The results of the investigation are presented below.

[Investigation method]

1) Data period: April 2016 to March 2017 (1 year)
2) Patient's age: Less than 20 years (Age as of the end of March 2017)
3) Data extraction
   - 3-1) Antimicrobial drugs that contain pivoxil, with their trade name (abbreviated) within parentheses
     - Penicillin antimicrobial drugs: Pivmecillinam hydrochloride (marketing discontinued in 2013)
     - Third-generation cephem antimicrobial drugs: Cefcapene pivoxil hydrochloride hydrate (Flomox, etc.), Cefditoren pivoxil (Meiact MS, etc.), Cefteram pivoxil (Tomiron, etc.)
     - Carbapenem antimicrobial drugs: Tebipenem pivoxil (Orapenem)
   - 3-2) Diagnostic names for carnitine deficiency
     - Carnitine deficiency, primary carnitine deficiency, secondary carnitine deficiency, carnitine insufficiency, suspected carnitine insufficiency
   - 3-3) Carnitine replacement therapy, with their trade name (abbreviated) within parentheses
     - Levocarnitine preparation (L-Cartin FF)

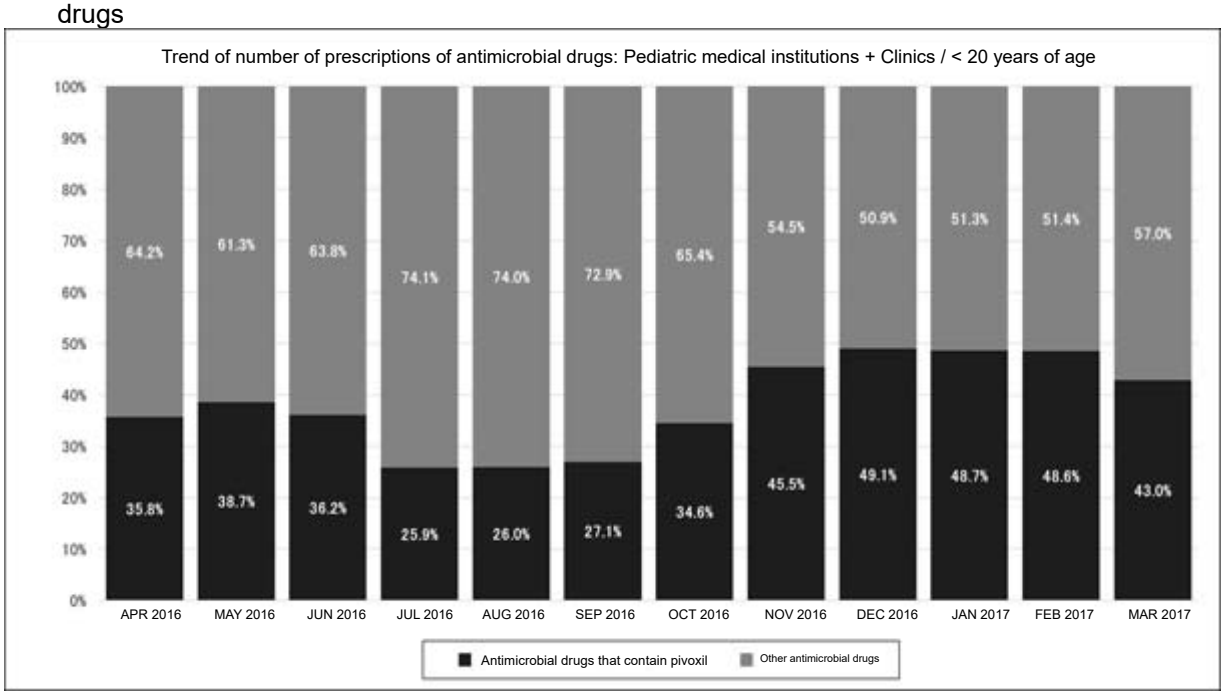
[Investigation results]

3-1. Actual prescription practices with antimicrobial drugs that contain pivoxil (number of prescriptions)

Age group	Age	Third-generation cephem						Carbapenem antimicrobial agents		Penicillin antimicrobial agents		Total
		Cefcapene		Cefditoren		Cefteram		Tebipenem		Pivmecillinam		
		Fine granules for pediatric	Tablets	Fine granules for pediatric	Tablets	Fine granules for pediatric	Tablets	Fine granules for pediatric	Tablets	Fine granules for pediatric	Tablets	
Newborns/nursing infants	0	38	0	54	0	0	0	*	0	0	0	93
Toddlers and preschoolers	1	363	*	564	0	208	0	53	0	0	0	1,190
	2	671	0	1,284	0	410	0	168	0	0	0	2,533
	3	451	0	847	0	252	0	79	0	0	0	1,629
	4	494	3	819	*	251	*	62	0	0	0	1,632
	5	391	5	692	*	205	*	47	0	0	0	1,342
	6	317	17	610	15	202	10	31	0	0	0	1,202
School-age children	7	229	66	409	66	170	31	13	0	0	0	984
	8	175	106	253	92	90	25	10	0	0	0	751
	9	140	159	139	124	106	29	7	0	0	0	704
	10	107	177	97	144	68	31	4	0	0	0	628
	11	71	168	59	165	56	49	*	0	0	0	569
	12	39	127	34	171	32	54	0	0	0	0	457
	13	23	102	39	155	21	50	4	0	0	0	394
	14	6	94	18	160	0	57	0	0	0	0	335
15 to < 20 years	15	6	73	6	106	*	30	0	0	0	0	223
	16	8	47	17	70	4	21	0	0	0	0	167
	17	6	69	11	61	0	19	0	0	0	0	166
	18	6	49	19	41	*	15	0	0	0	0	131
	19	5	38	*	25	0	12	0	0	0	0	81
Total		3,546	1,302	5,972	1,397	2,078	436	480	0	0	0	15,211

During the data period of this investigation, the total number of prescriptions for administration of antimicrobial drugs that contain pivoxil was 15 211 (8 062 patients). Cefcapene (Flomox, etc.) and cefditoren (Meiact MS, etc.) accounted for approximately 80% of prescriptions, and these drugs were mostly prescribed in fine granules for pediatric patients to toddlers and preschoolers. It is inferred that there were patients who had more than one prescription during the data period of this investigation, and as such the above numerical values (numbers of prescriptions) are cumulative numbers.

3-2. Proportions of prescriptions of antimicrobial drugs that contain pivoxil and other antimicrobial drugs



* Other antimicrobial drugs: Pharmaceutical products under YJ code - second classification code “61” (Antibiotics) other than antimicrobial drugs that contain pivoxil

During the data period of this investigation, antimicrobial drugs that contain pivoxil were also frequently prescribed.

3-3. Antimicrobial drugs that contain pivoxil and carnitine deficiency (number of patients)

Pivoxil drug prescribed			Yes				No			Total
Blood carnitine fraction test			Yes		No		Yes		No	
Carnitine deficiency diagnosed			Yes	No	Yes	No	Yes	No	Yes	
Carnitine replacement therapy prescribed			Yes	No	Yes	No	Yes	No	Yes	
Age group/age	Newborns/nursing infants	0	0	*	0	60	0	0	0	61
	Toddlers and preschoolers	1	0	0	*	657	0	0	0	658
		2	0	*	*	1,059	0	0	0	1,062
		3	0	0	6	796	0	0	0	802
		4	0	0	*	841	0	0	0	843
		5	*	0	6	676	0	0	0	683
		6	0	*	3	632	0	0	*	638
	School-age children	7	*	0	*	538	0	0	0	541
		8	0	0	0	459	0	0	0	459
		9	0	0	*	418	0	0	0	419
		10	*	*	3	376	0	0	0	381
		11	0	0	*	345	0	0	0	347
		12	0	0	*	278	0	0	0	279
		13	0	0	4	231	0	0	0	235
		14	0	0	*	202	0	0	0	203
	15 to < 20 years	15	0	0	*	154	0	0	0	155
		16	0	0	0	111	0	0	0	111
		17	0	0	4	101	0	0	0	105
		18	0	*	*	73	0	0	0	76
		19	0	0	0	55	0	0	0	55
Total			3	7	40	8,062	0	0	*	8,113

As for the number of blood carnitine fraction tests, 28 tests were performed in 10 patients, and results were confirmed for 21 tests. The blood carnitine level was lower than the normal range for 12 tests in 4 patients. Insurance coverage was applied to blood carnitine fraction tests in February 2018. The possibility that the data period prior to the insurance coverage affected the results cannot be ruled out.

The number of cases diagnosed with carnitine deficiency was high in toddlers and preschoolers, and more than 90% of the cases were from pediatric medical institutions. Also, regarding carnitine replacement therapy, many of the patients with a disease name associated with carnitine deficiency were toddlers and preschoolers, and consequently the number of prescriptions of L-Cartin FF oral solution 10% was the highest, accounting for approximately 75% of all cases.

Of the 8 062 patients who were prescribed antimicrobial drugs that contain pivoxil, 43 were diagnosed with carnitine deficiency regardless of the presence or absence of blood carnitine fraction tests and were prescribed carnitine replacement therapy. When the data of these 43 patients were further analyzed in-depth with a time-series perspective, the results suggested that the possibility of onset of carnitine deficiency due to prescription of antimicrobial drugs that contain pivoxil could not be ruled out in 7 patients.

The System is used on an individual patient basis and has no information shared across medical institutions; therefore, it is not adequate to conduct a complete time-series investigation. Nonetheless, the results of this investigation suggested the possibility of onset of carnitine deficiency in 7 (0.087%) of the 8 062 patients who were prescribed antimicrobial drugs that contain pivoxil.

Similarly to the investigation on influenza antiviral drugs, the data period for the investigation is 1 year; therefore, it is not adequate to assess adverse reactions to antimicrobial drugs that contain pivoxil based on these data. In the future, an extension of the period for data as well as a more in-depth analysis and continuous monitoring including active use of background information such as patients' past medical histories or complications and details of associated drug prescriptions will enable further contribution to enhancement of safety measures in the environments for use of pediatric pharmaceutical products.

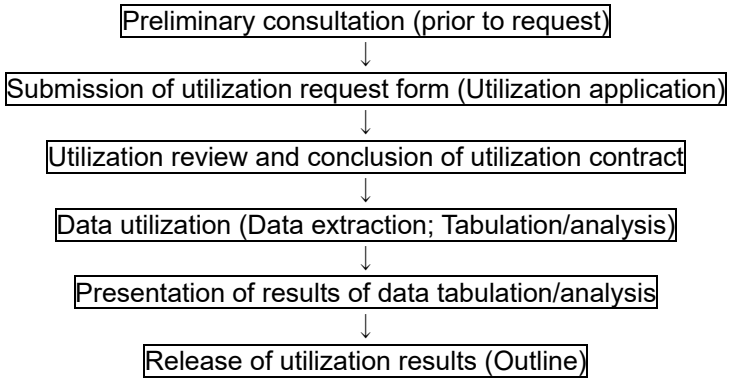
The results of the above-mentioned 2 investigations will be provided on the website of the Pediatric Medical Data Collecting System https://pharma-net.ncchd.go.jp/ (only in Japanese) later.

4. Efforts focused on future utilization of the System

Regarding utilization of data accumulated in the System, the Guidelines for Utilization of the Pediatric Medical Data Collecting System, which comprehensively address utilization application, utilization review, utilization contract, publication of utilization results, related forms, etc. have been prepared by the Review Conference on the Guidelines for Utilization of Data in the Pediatric Medical Data Collecting System since fiscal year (FY) 2017. Various written procedures (data security, data validation, quality control, back-up, etc.) necessary for the operation of the medical information database will be improved in a sequential manner.

A trial utilization is scheduled to start for researchers (academia) in FY 2020, pending final confirmation of the guidelines, preparation of various written procedures, and establishment of a utilization review committee.

<Currently assumed flow of data utilization (Outline)>



5. Closing Comments

In recent years, preparation of the environment has proceeded that enables a rapid grasp of information on the onset of adverse reactions, etc. by comprehensively collecting data of electronic medical chart information or health insurance claim information and managing those data in a unified manner. Development of technologies is sought which automatically enable primary assessments of adverse reactions to pharmaceutical products based on the information obtained from these huge amounts of data (big data). In many of the conventional assessments of adverse reactions, adverse reaction reports are collected and data on adverse reactions are assessed. It is hoped that new approaches to safety measures will be established if assessment of adverse reactions as mass data is realized by utilizing the System.

With respect to safety measures/development promotion and proper use in pediatric disciplines, the reality is far from perfect. We intend to further enhance safety measures for pediatric drugs and also contribute to their development through consolidation and analysis/assessment of information obtained from the System.

[References]

1) Pharmaceuticals and Medical Devices Safety Information No. 369 (January 9, 2020)
2) PMDA Alert for Proper Use of Drugs: Pharmaceuticals and Medical Devices Agency No. 8 (April 2012)
3) Precaution concerning hypocarnitinaemia related to the dosing of antimicrobial drugs that contain pivoxil: Regulatory Affairs Committee of Japan Pediatric Society (July 2019)

<Acknowledgment>

We are deeply grateful to relevant persons at pediatric medical institutions and clinics who have cooperated in the introduction of the System and persons who have been involved in the designing/creation of the System.

2
Handling of Relative Contraindications associated with Revision of Instructions for Package Inserts of Prescription Drugs

1. Introduction

Regarding the instructions for package insert language for prescription drugs, a notification of new instructions was issued in June 2017 and switching over to package inserts in line with the new instructions has been proceeding since April 2019 with those processed.

Major revisions under the new instructions include abolition of the Relative Contraindications section and new addition of the Precautions concerning Patients with Specific Backgrounds section.

While entries in the Relative Contraindications section will mostly shift to the Precautions concerning Patients with Specific Backgrounds section, shifting to the Contraindication section is considered proper for some of the entries. To address the issue, entries in the Relative Contraindications section in the package inserts prepared under the old instructions (Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997) were reviewed concerning; whether corresponding entries are listed in the Contraindications section of overseas package inserts, whether the entries are listed in the Contraindications section of the Japanese package inserts of similar drugs, or whether related Japanese and overseas guidelines describe the entries as subject to Contraindication. Then, together with the solicited opinions of the marketing authorization holders (MAHs), the issue was brought to and discussed in the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter “the Subcommittee on Drug Safety). This section will introduce the revision of the package inserts implemented based on the discussion.

The Pharmaceuticals and Medical Devices Safety Information No. 344 (issued in June 2017) and No. 360 (February 2019) outlined the revision of instructions for package inserts under the new instructions.

Active Ingredient	Date of the Subcommittee on Drug Safety
Amobarbital, secobarbital sodium, pentobarbital calcium	March 11, 2019
Sodium valporate	
Hydroxyethylated starch 70000	
Penicillamine	
Cephem, peniciline, glycopeptide antibiotics, penem antibiotics, carbapenem antibiotics	
Phenylephrine hydrochloride, etilephrine hydrochloride	June 26, 2019
Ozagrel sodium	
Suxamethonium chloride hydrate	
Purified tuberculin	
Urokinase	October 29, 2019

2. Details of the discussion in the Subcommittee on Drug Safety by active ingredient

For the drug products involving the 17 ingredients reviewed for their current entries in the Relative Contraindications section, opinions of academic societies related to the specialties that mainly use the drugs were solicited in association with the shift of the reviewed entries to the Contraindications section. Based on the solicited opinions of related academic societies that considered the actual usage of the drugs in clinical practices, revision of package insert was drafted

and discussed in the Subcommittee on Drug Safety. Entries that shift to the Contraindication were considered appropriate were moved from the Relative Contraindications section to the Contraindications section based on the Revisions of Precautions (PSEHB/PSD No. 0328-1, dated March 28, 2019, PSEHB/PSD No. 0717-1, dated July 17, 2019, PSEHB/PSD No. 1112-1, dated November 12, 2019).

Revisions for Individual products will be outlined in the subsequent pages.

(1) Amobarbital, secobarbital sodium, pentobarbital calcium

a. Date of the Subcommittee on Drug Safety	March 11, 2019
b. Indications	・Amobarbital: insomnia, sedation of anxiety and tense ・Secobarbital sodium: insomnia, anesthetic premedication, induction of systemic anesthesia, sedation of anxiety and tense ・Pentobarbital calcium: insomnia, anesthetic premedication, sedation of anxiety and tense, sleep regulation in continuous sleep therapy
c. Relative Contraindications subject to the revision	Patients with acute intermittent Porphyria
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindication
e. Reason for the decision that Contraindication is appropriate	・Contraindicated in the overseas package inserts ・Contraindicated in the package inserts of similar drugs ・Contraindicated in related guidelines
f. Opinions of related academic societies	・The Japanese Society of Psychiatry and Neurology: No objection to the proposed revision(s) ・Japanese Society of Anesthesiologists: considers the decision on revisions appropriate.
Date of the notification of revisions of precautions	March 28, 2019

(2) Sodium valporate

a. Review in the Subcommittee on Drug Safety	March 11, 2019
b. Indications	・Treatment of various types of epilepsy (petit mal, focus seizure, psychomotor seizures, and mixed seizure) and personality or behaviour disorder (bad mood, irritability, etc.) associated with epilepsy ・Treatment of mania, manic state in manic depressive illness ・Prophylaxis of migraine attacks
c. Relative Contraindications subject to the revision	Pregnant women or women who may be pregnant
d. Results of deliberation at the Subcommittee of Drug Safety	The drug should be contraindicated for the use as “prophylaxis of migraine attacks (which does not apply to the use for the treatment of various types of epilepsy [petit mal, focus seizure, psychomotor seizures, and mixed seizure], personality or behaviour disorder [bad mood, irritability, etc.] associated with epilepsy and mania and manic state in manic depressive illness).
e. Reason for the decision that Contraindication is appropriate	・Contraindicated in the overseas package inserts
f. Opinions of related academic societies	・The Japan Epilepsy Society: supports the opinion regarding epilepsy. ・The Japanese Society of Psychiatry and Neurology: The drug should not be contraindicated for the use in “mania and manic state in manic depressive illness”. ・The Japanese Society of Neurology: supports the opinion regarding migraine. ・The Japanese Headache Society: supports the opinion regarding migraine.
Date of the notification of revisions of precautions	March 28, 2019

(3) Hydroxyethylated starch 70000

a. Review in the Subcommittee on Drug Safety	March 11, 2019
b. Indications	・Excessive bleeding across medical specialties ・Blood diluent for extracorporeal circulation
c. Relative Contraindications subject to the revision	Patients with a history of hypersensitivity such as rash
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindication
e. Reason for the decision that Contraindication is appropriate	・Contraindicated in the package inserts of similar drugs
f. Opinions of related academic societies	・Japanese Society of Anesthesiologists: considers the decision on revisions appropriate.
Date of the notification of revisions of precautions	March 28, 2019

(4) Penicillamine

a. Review in the Subcommittee on Drug Safety	March 11, 2019
b. Indications	・Rheumatoid arthritis ・Wilson disease (hepato-lenticular degeneration) ・Lead, mercury, copper poisoning
c. Relative Contraindications subject to the revision	For indication of rheumatoid arthritis: Patients with decreased bone marrow function
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindications
e. Reason for the decision that Contraindications section is appropriate	・Contraindicated in the overseas package inserts ・Contraindicated in the package inserts of similar drugs
f. Opinions of related academic societies	・Japan College of Rheumatology: supports the opinion
Date of the notification of revisions of precautions	March 28, 2019

(5) Cephem antibiotic, penicillin antibiotics, glycopeptide antibiotics, penem antibiotics, carbapenem antibiotics

a. Date of the Subcommittee on Drug Safety	March 11, 2019
b. Indications	・Infectious diseases
c. Relative Contraindications subject to the revision	Patients with a history of hypersensitivity to any of the ingredients of this drug (or XX antibiotics)
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindicated for “Patients with a history of hypersensitivity to ‘any of the ingredients of this drug’”
e. Reason for the decision that Contraindication is appropriate	(for some of these antibiotics) ・Contraindicated in the overseas package inserts ・Contraindicated in the package inserts of similar drugs
f. Opinions of related academic societies	・Japanese Society of Chemotherapy: No different opinions to mention ・The Japanese Association for Infectious Diseases: No problems
Date of the notification of revisions of precautions	March 28, 2019

(6) Phenylephrine hydrochloride, etilefrine hydrochloride

a. Date of the Subcommittee on Drug Safety	June 26, 2019
b. Indications	Phenylephrine hydrochloride ・Adjuvant treatment in acute hypotension or shock associated with various diseases or conditions ・Paroxysmal supraventricular tachycardia ・Prolongation of effects in local anesthesia Etilefrine hydrochloride ・Adjuvant treatment in acute hypotension or shock associated with orthostatic hypotension, various diseases or conditions
c. Relative Contraindications subject to the revision	Patients with a history of hypersensitivity to any of the ingredients of this drug
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindication
e. Reason for the decision that Contraindication is appropriate	・Contraindicated in the overseas package inserts
f. Opinions of related academic societies	・The Japanese Circulation Society: No objections to the proposed revision
Date of the notification of revisions of precautions	July 17, 2019

(7) Ozagrel sodium

a. Review in the Subcommittee on Drug Safety	June 26, 2019
b. Indications	・Improvement of cerebrovascular spasm after subarachnoid hemorrhage surgery and accompanying cerebral ischemia ・Improvement of movement disorder associated with cerebral thrombosis (acute phase)
c. Relative Contraindications subject to the revision	Patients with major infarction accompanied by seriously disturbed consciousness
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindication
e. Reason for the decision that Contraindication is appropriate	・Required precaution is considered in place in the current Contraindication entries.
f. Opinions of related academic societies	・Japan College of Rheumatology: supports the proposed revision
Date of the notification of revisions of precautions	July 17, 2019

(8) Suxamethonium chloride hydrate

a. Date of the Subcommittee on Drug Safety	June 26, 2019
b. Indications	・Muscle relaxing in anesthesia ・Muscle relaxing in endotracheal intubation, fractures or dislocation, and laryngospasm ・Muscle relaxing in electroconvulsive therapy ・In the diagnosis of abdominal mass
c. Relative Contraindications subject to the revision	Patients with a history of severe burn, extensive crush injury, uraemia, quadriplegia, or digitalis intoxication or patents recently administered digitalis
d. Results of deliberation at the Subcommittee of Drug Safety	This drug should be contraindicated for “patients with post-acute phase serious burn, post-acute phase extensive crush injury, or quadriplegia”
e. Reason for the decision that Contraindication is appropriate	・Contraindicated in the overseas package inserts ・Contraindicated in related guidelines
f. Opinions of related academic societies	Japanese Society of Anesthesiologists: concluded that the proposed revision was appropriate.
Date of the notification of revisions of precautions	July 17, 2019

(9) Purified tuberculin

a. Review in the Subcommittee on Drug Safety	June 26, 2019
b. Indications	Used In the diagnosis of tuberculosis
c. Relative Contraindications subject to the revision	・Persons with a history of extremely strong reactions after a tuberculin skin test such as blisters or necrosis ・In addition to the aforementioned persons, those in a condition inappropriate for tuberculin skin test
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindication
e. Reason for the decision that Contraindication is appropriate	・Contraindicated in the overseas package inserts ・Contraindicated in the package inserts of similar drugs
f. Opinions of related academic societies	The Japanese Association for Infectious Diseases, the Japanese Society for Tuberculosis, the Japanese Respiratory Society, Japan Pediatric Society, the Japanese Society for Internal Medicine: consider the proposed revision appropriate
g. Date of the notification of revisions of precautions	July 17, 2019

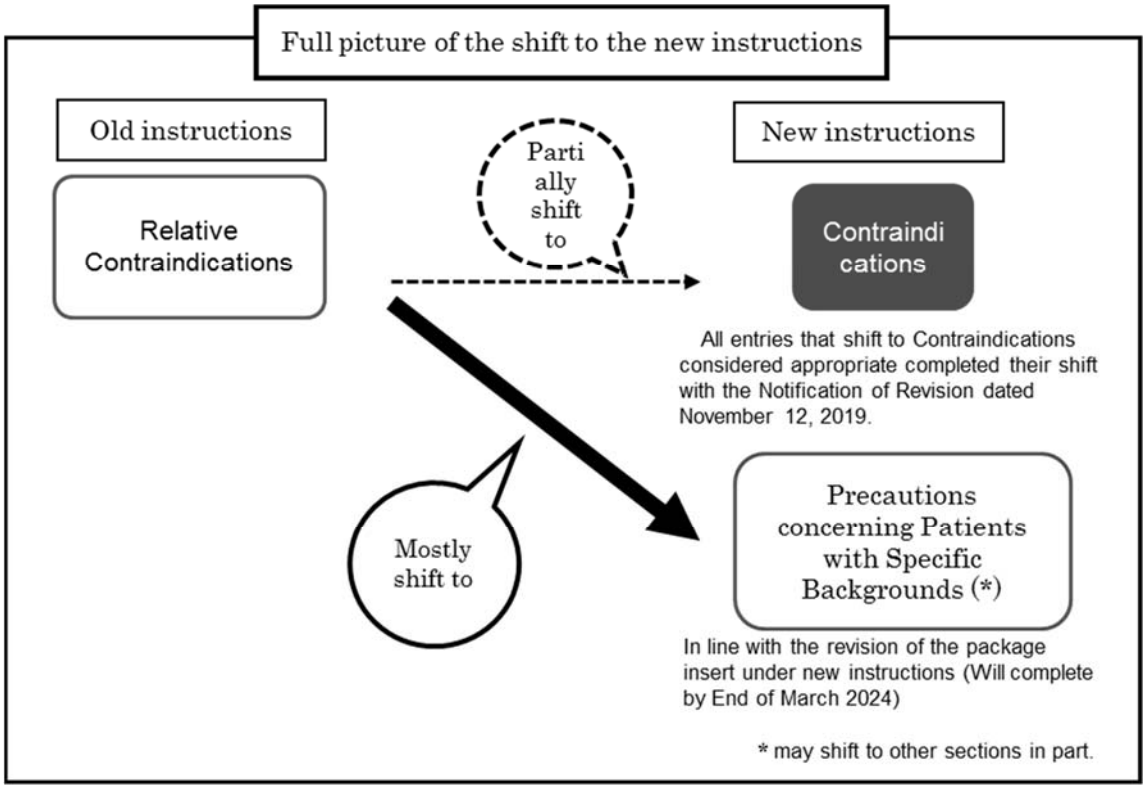
(10) Urokinase

a. Date of the Subcommittee on Drug Safety	October 29, 2019
b. Indications	Treatment of thrombosis/occlusive diseases as follows; ・Cerebral thrombosis (within 5 days after onset with no bleeding revealed by computerized tomogram) ・Peripheral artery/venous occlusion (within 10 days of onset)
c. Relative Contraindications subject to the revision	Patients with sudden onset of neurological symptoms
d. Results of deliberation at the Subcommittee of Drug Safety	Contraindication
e. Reason for the decision that Contraindication is appropriate	・The current Contraindications entry is considered the same intent. It was concluded that precaution is provided under the current Contraindications section.
f. Opinions of related academic societies	・The Japanese Circulation Society: supports the proposed revision. ・The Japanese Society of Psychiatry and Neurology: No objection to the proposed revisions ・The Japanese Circulation Society: supports the proposed revision.
g. Date of the notification of revisions of precautions	November 12, 2019

3. Closing remark

To date, of entries so far included in the Relative Contraindications section, all those for which shit to Contraindication was considered appropriate have all completed the shift.

Whereas, those entries that will not move to the Contraindications section will remain in the Relative Contraindications section in package inserts under the old instructions until they will move to the Precautions concerning Patients with Specific Backgrounds upon switching over to the package insert under the new instructions. Switching of package inserts to the new instructions will be carried out with those completed in line with consultation for revision, and since the transition period for the operation is extended to the end of March 2024, package inserts with Relative Contraindication entries will remain for a while. Medical professionals are requested to understand the intent of the revision of the revision of Relative Contraindications and further cooperate with proper use of medicines.



[Reference]

1) Pharmaceuticals and Medical Devices Safety Information No.344 Revision of Instructions for Package Inserts of Prescription Drugs

   https://www.pmda.go.jp/files/000218681.pdf

2) Pharmaceuticals and Medical Devices Safety Information No.360 Package Inserts of Prescription Drugs under the Revised Instructions

   https://www.pmda.go.jp/files/000227942.pdf

3) Material 1-1 to 1-7, the 12th FY 2018 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on March 11, 2019)

   https://www.mhlw.go.jp/stf/shingi2/0000183979_00002.html (only in Japanese)

4) Revision of Precautions (PSEHB/PSD Notification No. 0328-1, dated March 28, 2019)

   https://www.mhlw.go.jp/content/11120000/000494937.pdf (only in Japanese)

5) Material 2-1 to 2-6, the 4th FY 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on June 26, 2019)

   https://www.mhlw.go.jp/stf/newpage_05441.html (only in Japanese)

6) Revision of Precautions (PSEHB/PSD Notification No. 0717-1, dated July 17, 2019)
https://www.mhlw.go.jp/content/11120000/000528695.pdf (only in Japanese)

7) Material 2-1 to 2-3, the 9th FY 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on October 29, 2019)
https://www.mhlw.go.jp/stf/newpage_07535.html (only in Japanese)

8) Revision of Precautions (PSEHB/PSD Notification No. 1112-1, dated July November 12, 2019)
https://www.mhlw.go.jp/content/11120000/000565262.pdf (only in Japanese)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated February 25, 2020, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Rotigotine

Branded name (name of company)	Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg, 18 mg (Otsuka Pharmaceutical Co., Ltd.)
Therapeutic category	Antiparkinsonian agents, central nervous system agents-miscellaneous
Indications	Neupro patch 2.25 mg, 4.5 mg: •Parkinson's disease •Moderate to severe idiopathic restless legs syndrome Neupro patch 9 mg, 13.5 mg, 18 mg: •Parkinson's disease

PRECAUTIONS (revised language is underlined)

[Under old instructions]	
ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)	Rhabdomyolysis: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. Patients should be carefully monitored for signs of acute kidney injury due to rhabdomyolysis.
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 43-month period (April 2016 to October 2019) Cases involving rhabdomyolysis: 3 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 53 000 Japanese market launch: February 2013

Case summary 1

<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>No.</th></tr>
<tr><td>1</td><td>Male 80s</td><td>Restless legs syndrome (chronic renal failure)</td><td>2.25 mg for 28 days
↓
4.5 mg for 22 days</td><td>
Elevated CPK and myoglobin
Day 1 of administration: The patient experienced unpleasant sensations in the legs. Administration of rotigotine 2.25mg/day was started.
Day 12 of administration: CPK elevated to 439 IU/L.
Day 29 of administration: The dose was increased to 4.5 mg/day.
Day 47 of administration: CPK elevated to 4 832 U/L (highest).
Date unknown: Results of blood tests were checked and clinical symptoms were checked with the patients who complained of fatigue and malaise.
On day 50 of administration: (day of discontinuation): Administration of rotigotine was discontinued.
1 day after discontinuation: Myoglobin elevated to 4 131 ng/mL.
Date unknown: While elevation in CPK and myoglobin was noted, the patient only experienced malaise and weakness without any symptoms of rhabdomyolysis such as myalgia or muscle weakness._
88 days after discontinuation: CPK returned to 180 U/L (normal).
Date unknown: The outcome of myoglobin elevation was “recovery".
</td></tr>
<tr><td colspan="5">
Laboratory test values
<table>
<tr><th></th><th>45 days before administration</th><th>17 days before administration</th><th>Day 12 of administration</th><th>Day 47 of administration</th><th>1 day after discontinuation</th><th>8 days after discontinuation</th><th>25 days after discontinuation</th><th>88 days after discontinuation</th></tr>
<tr><td>CPK (U/L)</td><td>143</td><td>154</td><td>439</td><td>4 832</td><td>—</td><td>539</td><td>459</td><td>180</td></tr>
<tr><td>Myoglobin (ng/mL)</td><td>—</td><td>—</td><td>—</td><td>—</td><td>4 131</td><td>—</td><td>—</td><td>—</td></tr>
</table>
</td></tr>
<tr><td colspan="5">Concomitant medications: Benidipine hydrochloride, doxazosin mesilate, furosemide, epinastine hydrochloride, amlodipine besilate, ferric citrate hydrate, metoclopramide, ketoprofen, olmesartan medoxomil, esomeprazole magnesium hydrate, nalfurafine hydrochloride, triazolam</td></tr>
</table>

Case summary 2

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose administration duration</th><th>Adverse reactions</th></tr>
<tr><th>Sex/ age</th><th>Reason for use (complication)</th><th>Clinical course and treatment provided</th></tr>
<tr><td>2</td><td>Male 80s</td><td>Parkinson's disease (hypertension, diabetes melitus, hyperlipidemia, idiopathic normal pressure hydrocephalus</td><td>4.5 mg for 4 days</td><td>Suspected rhabdomyolysis
Day 1 of administration: Administration of rotigotine 4.5 mg/day started.
Day 4 of administration (day of discontinuation): The patient’s posture was tilted to the right during rehabilitation. Difficulty in walking emerged. The patient experienced difficulty in keeping posture and muscle pain subsequently. Muscle weakness was also noted. CT imaging test showed no abnormalities. CPK elevated to 2 537 U/L in blood test. Suspected rhabdomyolysis developed. Administration of rotigotine was discontinued. An infusion electrolyte (maintenance fluid), furosemide injection started.
10 days after discontinuation: CPK declined to 135 IU/L in blood test and infusion electrolyte was discontinued. The outcome of the suspected rhabdomyolysis was “recovery”.</td></tr>
</table>

Laboratory test values

	21 days before administration	11 days before administration	Day 4 of administration (day of discontinuation)	1 day after discontinuation		2 days after discontinuation	4 days after discontinuation	10 days after termination
				First	Second			
CPK (IU/L)	140.0	140.0	2357.0	2357.0	2675.0	2846.0	1812.0	135.0
AST (IU/L)	31	—	95	106		127	97	35
ALT (l IU/L)	34	—	25	47		43	31	45
BUN (mg/dL)	19.2	—	25.3	22.6		23.1	17.8	17.5
Creatinine (mg/dL)	1.1	—	1.1	1.1		1.0	1.0	1.0

Concomitant medications: Fursultiamine B2/B6/B12, zonisamide, allopurinol, cilnidipine, ticlopidine hydrochloride, pravastatin sodium, torasemide, levodopa/carbidopa hydrate, voglibose, silodosin, imidafenacin, isosorbide dinitrat, ketoprofen

2 Aminolevulinic acid hydrochloride

Branded name (name of company)	Alaglio Divided Granules 1.5 g (SBI Pharmaceuticals Co., Ltd.)
Therapeutic category	Intracorporeal diagnostic agents-miscellaneous
Indications	Visualization of non-muscle invasive bladder cancer during transurethral resection of the bladder tumor

PRECAUTIONS (revised language is underlined)

[Under old instructions] ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)	**Hypotension:** Hypotension may occur. Patients should be carefully monitored and appropriate measures should be taken if any abnormalities are observed. Cases of hypotension prolonged after surgery have been reported in which continuous administration of vasopressor was required.
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 2-year period (December 2017 to November 2019) Cases involving hypotension: 15 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 000 Japanese market launch: December 2017

Case summary

No.	Patient		Daily dose administration duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and treatment provided
1	Female 80s	Visualization of non-muscle invasive bladder cancer (none)	20mg/kg for 1 day	**Hypotension** History: Hypertension, hypertrophic cardiomyopathy, total left ureterorenoscopy, caesarean section Day 1 of administration (day of onset): Blood pressure was 134/94 mmHg. Aminolevulinic acid hydrochloride was administered. Amlodipine besilate, atenolol was withdrawn on the day. 2 hours and 30 minutes after administration: The patient was admitted to the operation room. Blood pressure was 114/61 mmHg. No decrease was observed. 2 hours and 55 minutes after administration: Spinal subarachnoid anesthesia was performed with 0.5% hyperbaric bupivacaine hydrochloride hydrate (2.2 mL) 3 hours and 8 minutes after administration: Midazolam 1 mg was used. Blood pressure decreased to 67/40 mmHg. Pulse rate was 55/min. Despite the use of plasma substitute 500 mL, ephedrine hydrochloride 20 mg in total, and extracellular fluid 1 L, upward blood pressure response was poor. Sustained administration of phenylephrine hydrochloride started in a low head posture. Time is unknown.: Blood pressure was still in the 70 mmHg after the operation. An artery catheter (A-Line) and a central venous catheter were placed to administer noradrenaline 0.1 μg/kg/min in a sustained manner. Time is unknown.: The patient was allowed to return to the ICU when her blood pressure decreased to 114/63 mmHg. Time is unknown.: Noradrenaline was discontinued at night. 1 day after administration: The outcome was “recovery”. Blood pressure was 121/54 mmHg.
	Suspected concomitant medication: Bupivacaine hydrochloride hydrate Concomitant medications: Midazolam, amlodipine besilate, febuxostat, atenolol			

4
Revision of Precautions (No.311)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated February 25, 2020.

1 Antiparkinsonian agents, Central nervous system agents-miscellaneous
Rotigotine

Branded name	Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg, 18 mg (Otsuka Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Rhabdomyolysis**: Rhabdomyolysis characterized by myalgia, feelings of weakness, increased CK (CPK), increased blood myoglobin, and increased urine myoglobin may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. Patients should be carefully monitored for signs of acute kidney injury due to rhabdomyolysis.

2 Gout preparations
Allopurinol

Branded name	Zyloric Tablets 50, 100 (Glaxo Smith Kline K.K.), and the others
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Aseptic meningitis**: Aseptic meningitis accompanied by symptoms such as nuchal rigidity, pyrexia, headache, nausea and vomiting, or disturbed consciousness may occur. Cases of aseptic meningitis that developed several hours after the administration of this drug have been reported.
[Under New instructions]	
11. ADVERSE REACTIONS (newly added)	**Aseptic meningitis**: Aseptic meningitis accompanied by symptoms such as nuchal rigidity, pyrexia, headache, nausea and vomiting, or disturbed consciousness may occur. Cases of aseptic meningitis that developed several hours after the administration of this drug have been reported.

3 Antineoplastics-miscellaneous

Arsenic trioxide

Branded name Trisenox Injection 10 mg (Nippon Shinyaku Co., Ltd.)

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)

Wernicke's encephalopathy: Wernicke's encephalopathy may occur. Patients should be carefully monitored and if symptoms such as disturbed consciousness, ataxia, and eye movement disorder are observed, vitamin B1 measurement and imaging diagnostic assessment using MRI should be performed and appropriate measures should be taken such as administration of vitamin B1 and discontinuing this drug.

4 Antivirals

[1] Asunaprevir
[2] Glecaprevir hydrate/pibrentasvir
[3] Sofosbuvir
[4] Daclatasvir hydrochloride
[5] Ledipasvir acetonate/sofosbuvir

Branded name

[1] Sunvepra Capsules 100 mg (Bristol-Myers Squibb Company)
[2] Maviret Combination Tablets (AbbVie GK)
[3] Sovaldi Tablets 400 mg (Gilead Sciences Inc.)
[4] Daklinza Tablets 60 mg (Bristol-Myers Squibb Company)
[5] Harvoni Combination Tablets (Gilead Sciences Inc.)

[Under Old instructions]

Important Precautions (newly added)

Cases where a dose increase of warfarin or tacrolimus or a reduction of insulin or other antidiabetic agents due to hypoglycemia were required following initiation of a direct-acting antiviral(s) for hepatitis C have been reported. Dose adjustment for concomitant drugs may be required in association with anti-viral treatment with this drug. In particular, if patients on warfarin, tacrolimus or other drugs with a narrow therapeutic window that are metabolized by the liver, or on antidiabetic agents are initiated on this drug, their prescribing physicians of such drugs in principle should be informed of the initiation and the patients should be carefully monitored for their conditions through methods such as frequent monitoring of PT-INR, blood drug concentration, or blood sugar levels.

[Under New instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Cases where a dose increase of warfarin or tacrolimus or a reduction of insulin or other antidiabetic agents due to hypoglycemia were required following initiation of a direct-acting antiviral(s) for hepatitis C have been reported. Dose adjustment for concomitant drugs may be required in association with anti-viral treatment with this drug. In particular, if patients on warfarin, tacrolimus or other drugs with a narrow therapeutic window that are metabolized by the liver, or on antidiabetic agents are initiated on this drug, their prescribing physicians of such drugs in principle should be informed of the initiation and the patients should be carefully monitored for their conditions through methods such as frequent monitoring of PT-INR, blood drug concentration, or blood sugar levels.

*An investigation using MID-NET has been conducted (https://www.pmda.go.jp/files/000233987.pdf).

5 Aitivirals

[1] Elbasvir
[2] Grazoprevir hydrate

Branded name
[1] Erelsa Tablets 50 mg (MSD K.K.)
[2] Grazyna Tablets 50 mg (MSD K.K.)

[Under New instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Cases where a dose increase of warfarin or tacrolimus or a reduction of insulin or other antidiabetic agents due to hypoglycemia were required following initiation of a direct-acting antiviral(s) for hepatitis C have been reported. Dose adjustment for concomitant drugs may be required in association with anti-viral treatment with this drug. In particular, if patients on warfarin, tacrolimus or other drugs with a narrow therapeutic window that are metabolized by the liver, or on antidiabetic agents are initiated on this drug, their prescribing physicians of such drugs in principle should be informed of the initiation and the patients should be carefully monitored for their conditions through methods such as frequent monitoring of PT-INR, blood drug concentration, or blood sugar levels.

*An investigation using MID-NET has been conducted (https://www.pmda.go.jp/files/000233987.pdf).

6 Aitivirals

Sofosbuvir/velpatasvir

Branded name
Epclusa Combination Tablets (Gilead Sciences Inc.)

[Under Old instructions]

Important Precautions (newly added)

Cases where a dose increase of warfarin or tacrolimus or a reduction of insulin or other antidiabetic agents due to hypoglycemia were required following initiation of a direct-acting antiviral(s) for hepatitis C have been reported. Dose adjustment for concomitant drugs may be required in association with anti-viral treatment with this drug. In particular, if patients on warfarin, tacrolimus or other drugs with a narrow therapeutic window that are metabolized by the liver, or on antidiabetic agents are initiated on this drug, their prescribing physicians of such drugs in principle should be informed of the initiation and the patients should be carefully monitored for their conditions through methods such as frequent monitoring of PT-INR, blood drug concentration, or blood sugar levels.

[Under New instructions]

8. IMPORTANT PRECAUTIONS <common to all indications> (newly added)

Cases where a dose increase of warfarin or tacrolimus or a reduction of insulin or other antidiabetic agents due to hypoglycemia were required following initiation of a direct-acting antiviral(s) for hepatitis C have been reported. Dose adjustment for concomitant drugs may be required in association with anti-viral treatment with this drug. In particular, if patients on warfarin, tacrolimus or other drugs with a narrow therapeutic window that are metabolized by the liver, or on antidiabetic agents are initiated on this drug, their prescribing physicians of such drugs in principle should be informed of the initiation and the patients should be carefully monitored for their conditions through methods such as frequent monitoring of PT-INR, blood drug concentration, or blood sugar levels.

*An investigation using MID-NET has been conducted (https://www.pmda.go.jp/files/000233987.pdf).

7 Antivirals

Daclatasvir hydrochloride/asunaprevir/beclabuvir hydrochloride

Branded name Ximency Combination Tablets (Bristol-Myers Squibb Company)

[Under Old instructions]

Important Precautions (newly added)

Cases where a dose increase of warfarin or tacrolimus or a reduction of insulin or other antidiabetic agents due to hypoglycemia were required following initiation of a direct-acting antiviral(s) for hepatitis C have been reported. Dose adjustment for concomitant drugs may be required in association with anti-viral treatment with this drug. In particular, if patients on warfarin, tacrolimus or other drugs with a narrow therapeutic window that are metabolized by the liver, or on antidiabetic agents are initiated on this drug, their prescribing physicians of such drugs in principle should be informed of the initiation and the patients should be carefully monitored for their conditions through methods such as frequent monitoring of PT-INR, blood drug concentration, or blood sugar levels.

*An investigation using MID-NET has been conducted (https://www.pmda.go.jp/files/000233987.pdf).

8 Chemotherapeutics-miscellaneous

Fosravuconazole L-lysine ethanolate

Branded name Neupro patch 2.25 mg, 4.5 mg, 9 mg, 13.5 mg, 18 mg (Otsuka Pharmaceutical Co., Ltd.)

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)

Erythema multiforme: Erythema multiforme may occur. Patients should be carefully monitored and if any abnormalities are observed, appropriate measures should be taken such as discontinuing this drug.

9 Intracorporeal diagnostic agents-miscellaneous

Aminolevulinic acid hydrochloride

Branded name Alaglio Divided Granules 1.5 g (SBI Pharmaceuticals Co., Ltd.)
Alabel Oral 1.5 g (Nobelpharma Co., Ltd.)

[Under Old instructions]

Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)

Hypotension: Hypotension may occur. Patients should be carefully monitored and appropriate measures should be taken if any abnormalities are observed. Cases of hypotension prolonged after surgery have been reported in which continuous administration of vasopressor was required.

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 29 February, 2020)

◎: Products for which EPPV was initiated after February 1, 2020

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	pH4-Treated normal human immunoglobulin*1 Privigen 10% I.V. Drip Infusion 5g/50mL, 10g/100mL, 20g/200mL	CSL Behring K.K.	February 21, 2020
◎	Entrectinib*2 Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	February 21, 2020
◎	Modafinil*3 Modiodal Tablets 100 mg	Alfresa Pharma Corporation	February 21, 2020
◎	Doravirine Pifeltro Tablets 100 mg	MSD K.K.	February 17, 2020
◎	Insulin aspart (genetical recombination) Fiasp Injection FlexTouch, Fiasp Injection Penfill, Fiasp Injection 100 U/mL	Novo Nordisk Pharma Ltd.	February 7, 2020
	Dolutegravir sodium/lamivudine Dovato combination tablets	Viiv Healthcare K.K.	January 31, 2020
	Freeze-dried recombinant herpes zoster vaccine (prepared from Chinese hamster ovary cells) Shingrix for intramuscular injection	Glaxo Smith Kline K.K.	January 29, 2020
	Turoctocog alfa pegol (genetical recombination) Esperoct for i.v. injection 500, 1000, 1500, 2000, 3000	Novo Nordisk Pharma Ltd.	January 29, 2020
	Perampanel hydrate*4 Fycompa tablets 2 mg, 4 mg	Eisai Co., Ltd.	January 23, 2020
	Lascufloxacin hydrochloride Lasvic Tablets 75 mg	Kyorin Pharmaceutical Co.,Ltd.	January 8, 2020
	Nintedanib ethanesulfonate*5 Ofev capsules 100 mg, 150 mg	Boehringer Ingelheim Japan, Inc.	December 20, 2019
	Avelumab (genetical recombination)*6 Bavencio intravenous infusion 200 mg	Merck Biopharma Co., Ltd	December 20, 2019
	Ceftolozane sulfate/tazobactam sodium*7	MSD K.K.	December 20,

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Zerbaxa Combination for Intravenous Drip Infusion		2019
Certolizumab pegol (genetical recombination) *8 Cimzia 200 mg Syringe for S.C. Injection, Cimzia 200 mg AutoClicks for S.C. Injection	UCB Japan Co. Ltd.	December 20, 2019
Evocalcet*9 Orkedia Tablets 1 mg, 2 mg	Kyowa Kirin Co., Ltd.	December 20, 2019
Botulinum toxin type A Botox for injection 50 units, 100 units	Glaxo Smith Kline K.K.	December 20, 2019
Polyethylene glycol treated human normal immunoglobulin*10 Venoglobulin IH 5% I.V. 0.5 g/10 mL, 1g/20 mL, 2.5 g/50 mL, 5 g/100 mL, 10 g/200 mL, Venoglobulin IH 10% I.V. 0.5 g/5 mL, 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	Japan Blood Products Organization	December 20, 2019
Freeze-dried sulfonated human normal immunoglobulin*11 Kenketsu Venilon- I for Intravenous Injection 500 mg, 1000 mg, 2500 mg, 5000 mg	KM Biologics Co., Ltd.	December 20, 2019
Ropinirole hydrochloride Haruropi Tape 8 mg, 16 mg, 24 mg, 32 mg, 40 mg	Hisamitsu Pharmaceutical Co., Inc.	December 17, 2019
Omalizumab (genetical recombination) *12 Xolair for s.c. injection 75 mg, 150 mg, Xolair for s.c. injection syringe 75 mg, 150 mg	Novartis Pharma K.K.	December 11, 2019
Trafermin (genetical recombination) Retympa 250 μg Set for Otology	Nobelpharma Co., Ltd.	December 9, 2019
Burosumab (genetical recombination) Crysvita Subcutaneous Injection 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	December 6, 2019
Lisdexamfetamine mesilate Vyvanse Capsules 20 mg, 30 mg	Shionogi & Co., Ltd.	December 3, 2019
Vortioxetine hydrobromide Trintellix Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited.	November 27, 2019
Necitumumab (genetical recombination) Portrazza Injection 800 mg	Nippon Kayaku Co., Ltd.	November 22, 2019
Ranibizumab (genetical recombination) *13 Lucentis solution for intravitreal injection 10mg/mL	Novartis Pharma K.K.	November 22, 2019
Ixekizumab (genetical recombination) *14 Taltz Subcutaneous Injection Syringes 80 mg, Taltz Subcutaneous Injection Autoinjectors 80 mg	Eli Lilly Japan K.K.	November 22, 2019
Venetoclax Venclexta Tablets 10 mg, 50 mg, 100 mg	AbbVie GK	November 22, 2019
Safinamide mesilate	Meiji Seika Pharma Co.,	November 20,

Nonproprietary name / Branded name on	Name of the MAH	Date of EPPV initiate
Equfina Tablets 50 mg	Ltd.	2019
Roxadustat / Evrenzo tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 20, 2019
Ivabradine hydrochloride / Coralan Tablets 2.5 mg, 5 mg, 7.5 mg	Ono Pharmaceutical Co., Ltd.	November 19, 2019
Quizartinib hydrochloride / Vanflyta Tablets 17.7 mg, 26.5 mg	Daiichi Sankyo Co., Ltd.	October 10, 2019
Insulin degludec (genetical recombination)/liraglutide (genetical recombination) / Xultophy combination Injection FlexTouch	Novo Nordisk Pharma Ltd.	September 26, 2019
Belimumab (genetical recombination) / Benlysta for I.V. infusion 120 mg, 400 mg	Glaxo Smith Kline K.K.	September 20, 2019
Apremilast*15 / Otezla Tablets 10 mg, 20 mg, 30 mg	Celgene K.K.	September 20, 2019
Desmopressin acetate hydrate*16 / Minirinmelt OD Tablets 25 μg, 50 μg	Ferring Pharmaceuticals Co., Ltd.	September 20, 2019
Azithromycin hydrate / Azimycin Ophthalmic Solution 1%	Senju Pharmaceutical Co., Ltd.	September 11, 2019
Blonanserin / Lonasen Tape 20 mg, 30 mg, 40 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 10, 2019
Patisiran sodium / Onpattro infusion 2 mg/mL	Alnylam Pharmaceuticals, Inc.	September 9, 2019
Glycopyrronium bromide/formoterol fumarate hydrate / Bevespi Aerosphere 28 inhalations	AstraZeneca K.K.	September 4, 2019
Budesonide/glycopyrronium bromide/formoterol fumarate hydrate / Breztri Aerosphere 56 inhalations	AstraZeneca K.K.	September 4, 2019
Entrectinib / Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	September 4, 2019
Defibrotide sodium / Defitelio Injection 200 mg	Nippon Shinyaku Co., Ltd.	September 4, 2019
Ravulizumab (genetical recombination) / Ultomiris Intravenous Infusion 300 mg	Alexion Pharmaceuticals, Inc.	September 4, 2019

*1 Agammaglobulinemia or hypogammaglobulinemia

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

*3 Excessive daytime sleepiness associated with idiopathic hypersomnia

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

*5 Systemic sclerosis-associated interstitial lung disease

*6 Unresectable or metastatic renal cell carcinoma

*7 <applicable microorganisms> Zerbaxa-susceptible serratia bizio and haemophilus influenzae <applicable conditions> pneumonia and sepsis

*8 Plaque psoriasis, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma for which existing treatment methods are not sufficiently effective

*9 Hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy

*10 Preoperative desensitization in renal transplantation with donor-specific antibodies

*11 Acute optic neuritis (when steroids are not sufficiently effective)

*12 Seasonal allergic rhinitis (only in severe to the most severe cases inadequately controlled with existing treatment)

*13 Retinopathy of prematurity

*14 Ankylosing spondylitis with inadequate response to existing therapies

*15 Oral ulcers associated with Behçet's disease with inadequate response to local therapies

*16 Nocturia due to nocturnal polyuria in males