Pharmaceuticals and Medical Devices Safety Information

No. 331 March 2016

Table of Contents

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

Available information is listed here

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

Medi-navi is an email service that provides essential safety information released by the MHLW and PMDA. By registering, you can receive this information on the day of release.

Register here

Published by
Ministry of Health, Labour and Welfare

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

Pharmaceuticals and Medical Devices Safety Information

No. 331 March 2016

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 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, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DVT	Deep vein thrombosis
EPPV	Early post-marketing phase vigilance
MAH	Marketing authorization holder
PE	Pulmonary embolism
SJS	Stevens-Johnson syndrome
XML	Extensible Markup Language

1

"Children and Pharmaceuticals" Data Collecting Network Development Project

1. Practice of the use of pharmaceuticals for children

Recent remarkable progress of Life Innovation will promote research and development as well as supply of new drugs. It is very important to ensure the environment of safer use of pharmaceuticals for children, especially in view of supporting the development of the next generation.

However, it is very difficult to conduct clinical trials before approval of pharmaceuticals and to collect data for evaluation of safety and efficacy after the approval for children because of the limited population of target patients and dosage compared to those for adults.

1.1 Situation before approval (before marketing of the pharmaceuticals)

Clinical trial is a measure for collecting safety and efficacy data required for the approval of pharmaceuticals.

Collecting data from children is not the same as that from adults, since important conditions for assessing safety/efficacy (such as weight, height, maturity of each organ, etc.) varies widely in the case of growing children. Therefore, a clinical trial for children should be designed with much more careful consideration about each age group and status of growth compared to trials for adults.

In conducting clinical trials, pharmaceutical companies are not actively conducting clinical trials among children because of the low profitability and specificity of the target patients. It is also difficult for medical institutions to establish systems of clinical trials for children because of the limited number of clinical trials and cases of children.

1.2 Situation after approval (after marketing of the pharmaceuticals)

This applies to all pharmaceuticals, however, it is impossible to provide full safety data before approval, and information such as package inserts must be updated as needed by collecting/assessing adverse drug reaction (ADR) data, etc. after launch to ensure safe use of pharmaceuticals.

Necessary safety measures are adopted upon collecting voluntary case reports from healthcare professionals and marketing authorization holders (MAH) on ADR observed after launch. However, prompt gathering of necessary information is difficult given that the number of patients using the pharmaceutical is limited, and therefore, even if ADR occurs, reporting of such events will be even more limited.

In addition, it is difficult to figure out the frequency of ADR from voluntary case reports because the population of administered patients are uncertain even if the number of the ADR events are clear.

2. Objectives of the "Children and Pharmaceuticals" Data Collecting Network

Since 2012, in order to establish a system to collect/assess safety data of pharmaceuticals used in children based on the aforementioned background, the National Center for Child Health and Development has consolidated an information processing environment (i.e. data collecting system of pharmaceuticals for children) to collect data on administered dosage, laboratory testing on specimens, patients' conditions/symptoms, etc. when pharmaceuticals are administered to children and to create a database to manage and

analyze the data. This system utilizes networks such as the Japanese Association of Children's Hospitals and Related Institutions (**Diagram 1)**.

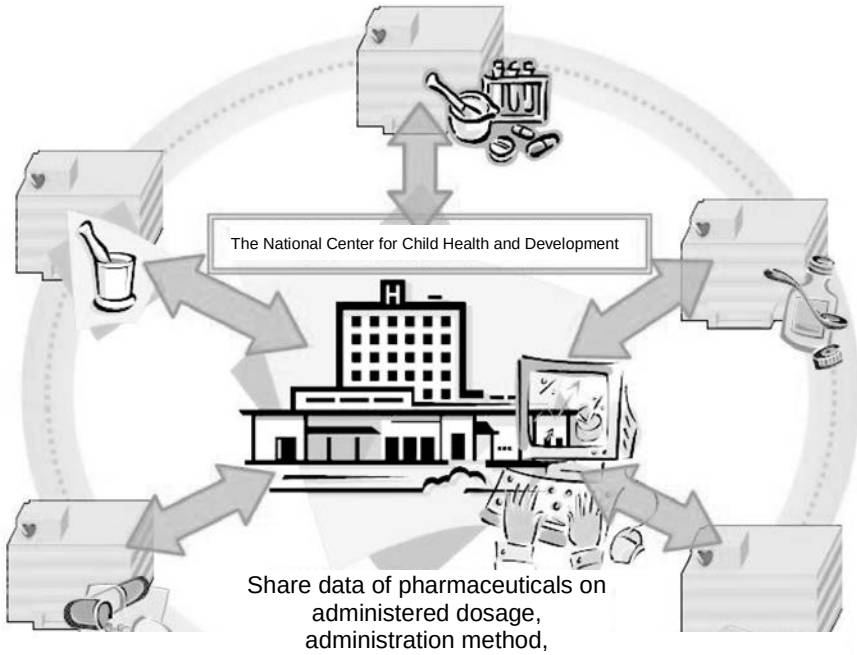

Diagram 1: Conceptual diagram of networks such as the Japanese Association of Children's Hospitals and Related Institutions

3. Current "Children and Pharmaceuticals" Data Collecting Network

The project for developing this network was started in 2012 and data has been collected since 2015.

This data collecting system of pharmaceuticals for children will be implemented in 11 children's hospitals and approximately 35 clinics; however, transmission and receipt of patient data has already been initiated sequentially in facilities that have completed preparations since 2015. As of February 29, 2016, information has been reported from 4 children's hospitals and 33 clinics. Data for approximately 140 000 patients have already been accumulated and are being updated on a daily basis.

The collected data enables comparison of the frequency of ADR based on the use of pharmaceuticals and comparison with other pharmaceuticals.

3.1 Detail of current function

Currently, it is possible to search and extract the collected data (**Diagram 2**).

Data regarding "interview", "diagnosis", "prescription/injection", and "laboratory testing" is collected, and it is possible to search these categories in combination with administered duration. Relevant patient data searched can be extracted in XML format (Extensible Markup Language format: a type of data description method). Furthermore, the extracted data can be converted to a different format for analysis. An automated analysis can then be conducted using a dataset formatted in a specific manner to assess the causal relationship between pharmaceuticals and ADR, which in turn can be used to automatically generate a report. The entire process has been automated.

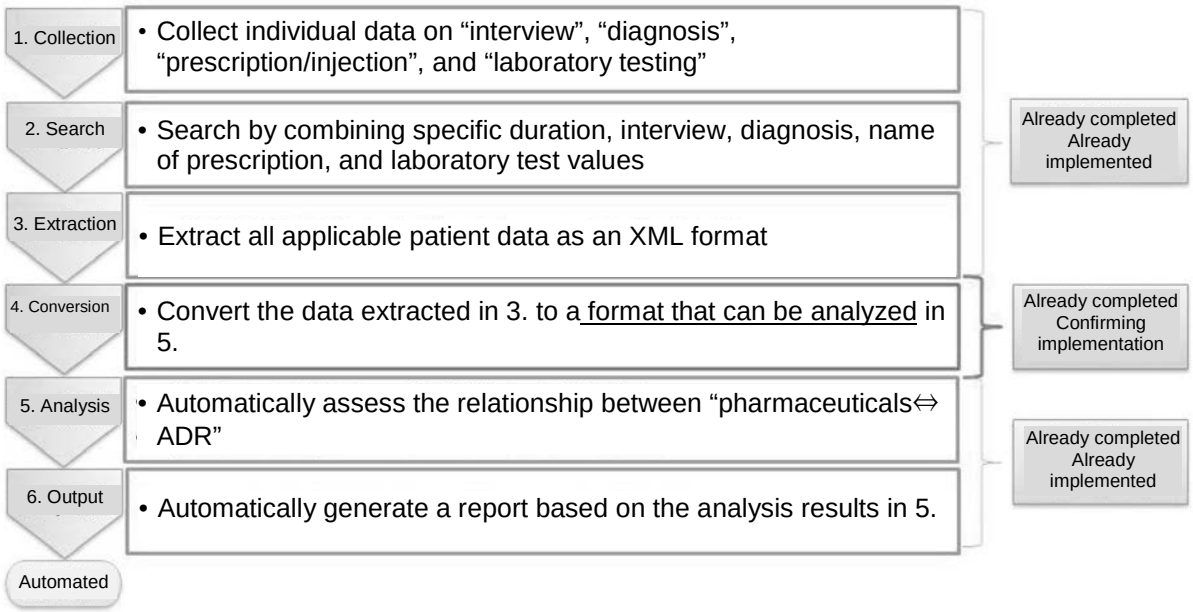

Diagram 2: Summary of current search/analysis function

4. Future plans

For the improvement of medical care for children, data collection system and progressive development of the function of the system will be pursued.

In regard to the function, information processing environment in terms of data analysis is currently being tested. Specifically, collection and practical use of the data related to changes in dosage forms, and improvement of the variety of totaling and reports are under consideration.

By collecting data related to pharmaceuticals for children and providing appropriate information to medical practice, safety measures of pharmaceuticals for children will be further improved.

2

Important Safety Information

Regarding the revision of the Precautions section of package inserts of pharmaceuticals in accordance with the Notification dated February 16, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Eribulin mesilate

Brand name (name of company)	Halaven Injection 1 mg (Eisai Co., Ltd.)
Therapeutic category	Antineoplastics-Miscellaneous
Indications	Unresectable or recurrent breast cancer

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Oculomucocutaneous syndrome (Stevens-Johnson syndrome [SJS]) and erythema multiforme: SJS or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference information

The number of reported adverse reactions (for which a causal relationship to the product could not be ruled out) for the past 3 years and 9 months (from April 2012 to December 2015).
Cases of SJS: 2 cases (no fatal case)
Cases of erythema multiforme: No case reported
The number of patients using this drug estimated by the MAH: Approximately 8 000 (from April 2014 to March 2015)
Launched in Japan: July 2011

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Recurrent breast cancer (None)	2 mg/body administered twice (once daily × 2)	**SJS** First cycle, first administration Treatment with eribulin mesilate 2 mg/body was started. 3 days after first administration: Occurrence of acneiform rash was confirmed. First cycle, second administration (Day of discontinuation): 2 mg/body of eribulin mesilate was administered. Aggravation of rash was noted after administration. 2 days after discontinuation: Acneiform rash was found on the patient's face and head, and the patient was referred to a dermatologist. 7 days after discontinuation: Redness and epidermal detachment was seen on the body trunk and both armpits; therefore, the patient

				was referred to a dermatologist once again. The patient presented with Nikolsky's sign, and the findings of the punch biopsy did not contradict that for SJS. Treatment with 500 mg/day methylprednisolone was initiated, and the same dosage was continuously administered until 9 days after discontinuation of administration. 10 days after discontinuation: The dosage of methylprednisolone was decreased to 50 mg/day. Although oral mucosal erosion was observed prior to administration of steroids, this was resolving after steroid mini-pulse therapy was administered. 12 days after discontinuation: Erythema in the body trunk disappeared, and it was determined that the patient had overcome the peak of the disease as no new blisters were observed. Gradual dose reduction of methylprednisolone was initiated after confirmation. SJS was resolving. 58 days after discontinuation: The patient died due to disease progression.
	Concomitant medications: mecobalamin, eszopiclone, furosemide, ursodeoxycholic acid, sulfamethoxazole/trimethoprim			

3

Revision of Precautions (No. 272)

This section presents details of revisions to the Precautions section of package inserts and brand names of pharmaceuticals that have been revised in accordance with the Notifications dated February 16, 2016.

1 Psychotropics

Methylphenidate hydrochloride

Brand name	Concerta Tablets 18 mg, 27 mg, and 36 mg (Janssen Pharmaceutical K.K.), Ritalin Tablets 10 mg and Ritalin Powder 1% (Novartis Pharma K.K.)
Adverse reaction (Clinically significant adverse reaction)	**Hepatic failure and hepatic function disorder:** Hepatic failure (including acute hepatic failure) or hepatic function disorder may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

2 Peptic ulcer agents

Esomeprazole magnesium hydrate

Brand name	Nexium Capsules 10 mg and 20 mg (AstraZeneca K.K.)
Adverse reaction (Clinically significant adverse reaction)	**Rhabdomyolysis:** Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feeling of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

3 Antivirals

Entecavir hydrate

Brand name	Baraclude Tablets 0.5 mg (Bristol-Myers K.K.)
Adverse reaction (Clinically significant adverse reaction)	**Hepatic function disorder:** Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may become elevated during treatment with this drug. If elevation in AST and ALT are observed, patients should be carefully monitored by conducting more frequent liver function tests, etc. If there are no signs of improvement in hepatic function based on test values, etc., appropriate measures such as discontinuation of administration should be adopted.

4

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of February 29, 2016)

◎: Products for which EPPV was initiated after January 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Eribulin Mesilate Halaven Intravenous Injection 1 mg[*1]	Eisai Co., Ltd.	February 29, 2016
◎	Risperidone Risperdal Tablets, 1 mg, 2 mg, Fine Granules 1 %, Risperdal OD Tablets 0.5 mg 1 mg, 2 mg, Risperdal Oral Solution 1 mg/mL[*2]	Janssen Pharmaceutical K.K.	February 29, 2016
◎	Rituximab（Genetical Recombination） Rituxan Injection 10 mg/mL[*3]	Zenyaku Kogyo Co., Ltd.	February 29, 2016
◎	Progesterone Utrogestan vaginal capsules 200mg	Fuji Pharma Co., Ltd.	February 18, 2016
◎	Indium pentetreotide (^{111}In) OctreoScan Kit for Intravenous Use	FUJIFILM RI Pharma Co., Ltd.	January 27, 2016
◎	Esflurbiprofen/Mentha oil Loqoa Tape	Taisho Pharmaceuticals Co., Ltd.	January 21, 2016
◎	Bosentan hydrate Tracleer 32 mg dispersible tablets for pediatrics	Actelion Pharmaceuticals Japan Ltd.	January 12, 2016
◎	Ozenoxacin Zebiax Lotion 2%	Maruho Co., Ltd.	January 7, 2016
	Vandetanib Caprelsa Tablets 100 mg	AstraZeneca K.K.	December 24, 2015
	Ciprofloxacin Ciproxan Intravenous Infusions 400 mg[*4]	Bayer Yakuhin, Ltd.	December 21, 2015
	infliximab (genetical recombination) Remicade Intravenous Infusions 100 mg[*5]	Mitsubishi Tanabe Pharma Corporation	December 21, 2015
	Apixaban Eliquis Tablets 2.5 mg, 5 mg[*6]	Bristol-Myers K.K.	December 21, 2015
	nivolumab (genetical recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*7]	Ono Pharmaceutical Co., Ltd.	December 17, 2015
	leuprorelin acetate Leuplin PRO Injections Kit 22.5 mg	Takeda Pharmaceutical Co., Ltd.	December 15, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
absorbed diphtheria-purified pertussis-tetanus- inactivated polio (salk vaccine) combined vaccine Square Kids Subcutaneous Injections Syringe	Kitasato Daiichi Sankyo Vaccine Co., Ltd.	December 9, 2015
venlafaxine hydrochloride Effexor SR Capsules 37.5 mg, 75 mg	Pfizer Japan Inc.	December 8, 2015
Trabectedin Yondelis Intravenous Infusions 0.25 mg, 1 mg	Taiho Pharmaceutical Co., Ltd.	December 7, 2015
Rivaroxaban Xarelto Fine Granules 10 mg, 15 mg[*8]	Bayer Yakuhin, Ltd.	December 7, 2015
None Miticure House Dust Mite Sublingual Tablets 3,300 JAU, 10,000 JAU	Torii Pharmaceutical Co., Ltd.	December 3, 2015
tiotropium bromide hydrate Spiolto Respimat 28 puffs	Nippon Boehringer Ingelheim Co., Ltd.	December 3, 2015
Lusutrombopag Mulpleta Tablets 3 mg	Shionogi & Co., Ltd.	December 1, 2015
Levetiracetam E Keppra Intravenous Infusions 500 mg	UCB Japan Co., Ltd.	December 1, 2015
insulin degludec (genetical recombination) / insulin aspart (genetical recombination) Ryzodeg FlexTouch	Novo Nordisk Pharma Ltd.	December 1, 2015
sucroferric oxyhydroxide P-TOL Chewable Tablets 250 mg, 500 mg	Kissei Pharmaceutical Co., Ltd.	November 27, 2015
ombitasvir hydrate/paritaprevir hydrate/ritonavir Viekirax Combination Tablets	AbbVie G.K.	November 26, 2015
glatiramer acetate Copaxone S.C. Injections 20 mg Syringe	Takeda Pharmaceutical Co., Ltd.	November 26, 2015
vildagliptin/metformin hydrochloride EquMet Combination Tablets LD and HD	Novartis Pharma K.K.	November 26, 2015
Omarigliptin Marizev Tablets 12.5 mg, 25 mg	MSD K.K.	November 26, 2015
None Actair House Dust Mite Sublingual Tablets 100 units (IR) and 300 units (IR)	Shionogi & Co., Ltd.	November 19, 2015
Ciprofloxacin Ciproxan Intravenous Infusions 200 mg[*9]	Bayer Yakuhin, Ltd.	September 24, 2015
Lamotrigine Lamictal Tablets for Pediatric Use 2 mg, 5 mg, Lamictal Tablets 25 mg, 100 mg[*10]	GlaxoSmithKline K.K.	September 24, 2015
Rivaroxaban Xarelto Tablets 10 mg, 15 mg[*11]	Bayer Yakuhin, Ltd.	September 24, 2015
olanexidine gluconate (1) Olanedine Antiseptic Solution 1.5% (2) Olanedine Solution 1.5% Antiseptic Applicator 10 mL (3) Olanedine Solution 1.5% Antiseptic Applicator 25 mL	Otsuka Pharmaceutical Co., Ltd.	September 16, 2015

Nonproprietary name Brand name on		Name of the MAH	Date of EPPV initiate
	dulaglutide (genetical recombination) Trulicity Ateos Subcutaneous Injection 0.75 mg	Eli Lilly Japan K.K.	September 16, 2015
	collagenase (clostridium histolyticum) Xiaflex Injection	Asahi Kasei Pharma Corporation	September 16, 2015
	antithrombin gamma (genetical recombination) Acoalan Injection 600	Kyowa Hakko Kirin Co., Ltd.	September 7, 2015
	hydroxychloroquine sulfate Plaquenil Tablets 200 mg	Sanofi K.K.	September 7, 2015
	insulin glargine (genetical recombination) Lantus XR Injection SoloStar	Sanofi K.K.	September 7, 2015
	ledipasvir acetonate/sofosbuvir Harvoni Combination Tablets	Gilead Sciences, Inc.	September 1, 2015
	talaporfin sodium Laserphyrin 100 mg Injection*12	Meiji Seika Pharma Co., Ltd.	September 1, 2015
	eliglustat tartrate Cerdelga Capsule 100 mg	Genzyme Japan K.K.	September 1, 2015

*1 Malignant soft tissue sarcoma
*2 Irritability associated with autism spectrum disorder in childhood
*3 Prophylaxis of antibody-related type rejection in the ABO blood group incompatibility transplant of kidney and liver transplants
*4 Pediatric indication and dosage
*5 Acute stage of Kawasaki's disease
*6 Treatment of venous thromboembolism [deep vein thrombosis (DVT) and pulmonary embolism (PE)], and reduction in the risk of recurrent DVT and PE
*7 Unresectable advanced/recurrent non-small cell lung cancer
*8 Treatment of DVT and PE, and reduction in the risk of recurrent DVT and PE
*9 Pediatric indication and dosage
*10 Typical absence seizures
*11 Treatment of DVT and PE, and reduction in the risk of recurrent DVT and PE
*12 Localized, residual recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy