Pharmaceuticals and Medical Devices Safety Information

No. 391 April 2022

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

Available information is listed here

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

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

Register here

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

Translated by
Pharmaceuticals and Medical Devices Agency

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

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Pharmaceuticals and Medical Devices Safety Information

No. 391 April 2022

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

ADR	Adverse drug reaction
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
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau

1
Revision of Precautions of Levonorgestrel (indicated for emergency contraception)

1. Introduction

Levonorgestrel tablets (hereinafter referred to as "this drug") was approved for marketing for the indication of "emergency contraception" on February 23, 2011. The 9.4 Patients with Reproductive Potential section of an electronic package insert of this drug states that "prior to administration of this drug, the absence of pregnancy should be adequately confirmed through methods such as a pelvic examination and immunoassay-based diagnosis of pregnancy." Also, the 9.5 Pregnant Women section states: "This drug should not be administered. If this drug is administered in the first or second trimester of pregnancy, external genital virilisation in female foetuses or feminisation of male foetuses may occur."

The relevant descriptions were revised on the basis of the deliberation at the 27th FY2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as "the Subcommittee on Drug Safety") held on Jan 24, 2022, and the details are introduced below.

2 Background

In July 2021, a consultation was requested to PMDA by Aska Pharmaceutical Co., Ltd., the marketing authorization holder of the brand name products of this drug (brand name: Norlevo Tablet 1.5 mg), who intended to make the following revisions regarding the electronic package insert of this drug.

- Regarding the description that "prior to administration of this drug, the absence of pregnancy should be adequately confirmed through methods such as a pelvic examination and immunoassay-based diagnosis of pregnancy," in the 9.4 Patients with Reproductive Potential section, "pelvic examination" should be deleted from the examples because it might cause a misunderstanding that "pelvic examination" is required as a method of confirming the absence of pregnancy.
- Regarding the description that "if this drug is administered in the first or second trimester of pregnancy, external genital virilisation in female foetuses or feminisation of male foetuses may occur," in the 9.5 Pregnant Women section, the relevant description should be deleted on the basis that "there are no epidemiological reports on the influence on the infants due to the use of this drug," etc. In addition, language should be added indicating that this drug is not effective in an existing pregnancy.

3. Deliberation by the Subcommittee on Drug Safety

(1) The influence on the infants in the case of the single-use of this drug for the purpose of emergency contraception during pregnancy

The results of the investigation of the statements in Japanese and overseas guidelines, overseas package inserts, published literature, etc. are as follows.

- In the Japanese and overseas clinical practice guidelines, etc., the description was found that there was no influence on the infants, and no description indicating an influence on the infants was found.
- As a result of reviewing the descriptions of overseas package inserts (US, UK, German, French, Canadian, and Australian), all of these package inserts state that "it is not suggested that the use of this drug can affect the infants" and that "this drug is not effective in an existing pregnancy." On the other hand, data were not sufficient to eliminate the possibility that the drug could have adverse effects on the infants and that non-clinical studies with levonorgestrel have shown virilisation of female fetuses at high doses.

- As a result of searching the published literature regarding an influence on the infants in pregnancies despite taking this drug, there were 9 related literature reports and studies (5 review reports, 3 observational studies, and 1 case report). It was described both in the review reports and observational studies that there was no influence on the infants.
- The case report indicated that intra-uterine death was noted. Still, it is considered difficult to conclude that the effect of this drug in this case report is drug-induced because the possibility that the events noted in the case report are accidental congenital anomaly due to causes other than the drug cannot be ruled out.
- Regarding the description that "if this drug is administered in the first or second trimester of pregnancy, external genital virilisation in female foetuses or feminisation of male foetuses may occur," in the 9.5 Pregnant Women section in the current electronic package insert, on the basis of the summaries of product applications for this drug at the time of application for marketing approval, there is a description that this language was placed with reference to the package inserts of other progesterone preparations (not indicated for emergency contraception) that had been approved at the time of application.

Following the above deliberation, the Subcommittee on the Drug Safety considered it appropriate to revise as follows regarding the 9.5 Pregnant Women section in the electronic package insert of this drug.

- The language should be added in the 9.5 Pregnant Women section indicating: "An observational study conducted overseas has reported that there were no differences in the incidence of foetal malformation, miscarriage, or any other adverse pregnancy outcomes in pregnancies despite taking levonorgestrel as an emergency contraceptive, compared with pregnancies without exposure to levonorgestrel." In addition, the language should be added to this section indicating that "this drug is not effective in an existing pregnancy."
- Concerning the current description indicating that "if this drug is administered in the first or second trimester of pregnancy, external genital virilisation in female foetuses or feminisation of male foetuses may occur," the information should be provided in the 15. OTHER PRECAUTIONS section with clarification that it is reported in other progesterone preparations (not drugs indicated for emergency contraception).

(2) Methods to confirm the absence of pregnancy

The results of the investigation of the statements in Japanese and overseas guidelines, overseas package inserts, published literature, etc. are as follows.

- As a result of reviewing the Japanese and overseas clinical practice guidelines, etc., there was no description indicating that a pelvic examination was necessary in any document. In addition, there was no description indicating that an immunoassay-based diagnosis of pregnancy was necessary in the Japanese and overseas clinical practice guidelines, etc. either.
- As a result of reviewing the current descriptions in the overseas package inserts, there was no description indicating that it was necessary to confirm the absence of pregnancy in the US, UK, German, and French package inserts. In the Canadian and Australian package inserts, it was stated that performing "a pregnancy test" and "pregnancy testing or pelvic examination," respectively, was recommended when pregnancy was suspected. However, there was no description regarding the tests that should be uniformly performed in the patients to whom this drug would be administered.

Given the above investigations and the following reasons, the Subcommittee on Drug Safety considered it appropriate to delete the examples of methods to confirm the absence of pregnancy (pelvic examination, immunoassay-based diagnosis of pregnancy) regarding the description that "prior to administration of this drug, the absence of pregnancy should be adequately confirmed through methods such as a pelvic examination and immunoassay-based diagnosis of pregnancy," in the 9.4 Patients with Reproductive Potential section in the electronic package insert of this drug.

- As shown in (1), the influence on the infants in case of single-use of this drug for the purpose of emergency contraception during pregnancy has not been suggested.
- This drug should be used within 72 hours after sexual intercourse. If it is required to uniformly perform the specific tests to confirm pregnancy, opportunities to use this dug may be missed.

- However, because "this drug is not effective in an existing pregnancy," as shown in (1), the Subcommittee on Drug Safety considered it still necessary to confirm the absence of pregnancy.

4. Closing remark

Healthcare professionals are requested to understand the gist of this revision and carefully check the electronic package insert for a careful decision when using levonorgestrel (indicated for emergency contraception). Continued cooperation by healthcare professionals for proper use of this drug would be appreciated.

[Reference]

・Materials 1-1 to 1-7 of the 27th FY 2021 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on Jan 24, 2022)
https://www.mhlw.go.jp/stf/newpage_23462.html (only in Japanese)

・Revision of PRECAUTIONS (PSEHB/PSD Notification No. 0203-1 dated Feb 3, 2022)
https://www.pmda.go.jp/files/000244755.pdf (only in Japanese)
English translation by PMDA (February 3, 2022)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0009.html

2
Digitization of Reports from Medical Professionals on Adverse Reactions/Infections/Malfunctions and Suspected Adverse Reactions [Information on the Report Reception Site]

1. Introduction

The PMDA receives reports on pharmaceuticals and medical devices safety information and reports on post-vaccination suspected adverse reactions from medical professionals as part of safety measure operations.

○ Pharmaceuticals and Medical Devices Safety Information Report

It is a system for medical professionals to report information on adverse health effects, etc. that develop as a result of use in clinical settings to the Minister of Health, Labour and Welfare pursuant to the Pharmaceuticals and Medical Devices Act[Note 1)] for drugs, medical devices, and cellular and tissue-based products[Note 2)]. Reported information is analyzed and evaluated from a professional perspective, and then necessary safety measures are taken, and also the information is provided to medical professionals widely and utilized to ensure post-marketing safety measures for drugs.

Note 1) Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)

Note 2) It is voluntary for quasi-drugs and cosmetics.

○ Reports on Post-vaccination Suspected Adverse Reactions

It is a system for physicians, etc. to report to the MHLW when they become aware of certain symptoms present in vaccinees pursuant to the Immunization Act[Note 3)]. Safety of vaccines is managed and reviewed based on collected information, and the information is provided to the general public widely and utilized to promote immunization administration.

Note 3) Immunization Act (Act No. 68 of 1948)

2. Digitization of Reports from Medical Professionals on Adverse Drug Reactions

Concerning various reports in 1., pharmaceuticals and medical devices safety information has been reported by FAX, post, or e-mail, and post-vaccination suspected adverse reactions have been reported by FAX so far.

The PMDA established an electronic reporting system via the website (hereinafter referred to as the "Report Reception Site") in April 2021 and started receiving electronic reports on adverse drug reactions and post-vaccination suspected adverse reactions. Medical professionals are able to electronically report also on medical devices, cellular and tissue-based products, quasi-drugs, and cosmetics using the Report Reception Site since April 1, 2022.

By using the Report Reception Site, medical professionals can report without having to prepare each report form.

3. Characteristics of the Report Reception Site

The Report Reception Site allows a series of operations from preparation of a report to submission to the PMDA to be completed efficiently and enables immediate reporting.

Electronic reports that use the Report Reception Site are less susceptible to risk of wrong transmission compared with the conventional reports by FAX, etc. and cyber security is also taken

into account in the site; therefore, it can be used reliably.

< Major features >
・The report under preparation can be temporarily saved and reloaded.
・Follow-up or similar case reports can be prepared using the Copy/Edit function of reports.
・As input support functions, some of the data can be input using a selection-type menu or a pull-down menu.
・Files such as laboratory test values (CSV format) can be loaded.
・For reports on post-vaccination suspected adverse reactions for which attaching a questionnaire is required, the questionnaire can also be input.
・A notification will be sent via e-mail upon completion of submission or receipt of reports.

4. Points to Note When Using the Report Reception Site

The questions most frequently asked on the Report Reception Site are explained below.

< Registration for use >

If you are using it for the first time, you need to register your user information such as your e-mail address in advance.

Please access the Report Reception Site page to go through the procedures.
(https://www.pmda.go.jp/safety/reports/hcp/0002.html)

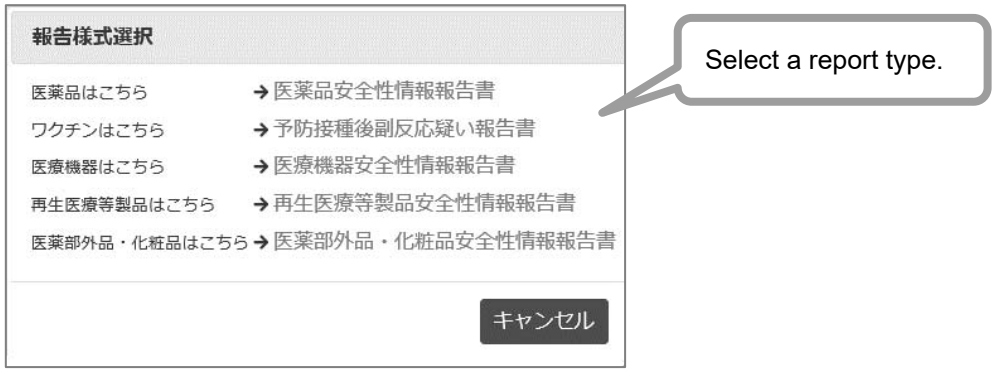
After registration is completed on the user information registration screen, a temporary password will be sent by e-mail. Please complete your definitive registration within 30 minutes from the temporary password being issued.

A registration for use is required separately from the registration for use of the PMDA Medi-navi.

Also, please note that the application destination for the registration for use is different.

< Report form selection screen> (This service is only available in Japanese.)

After logging in, press the "New" button on the report list screen, and then the report form selection screen will be displayed. Select a report type.



< Confirmation of entries >

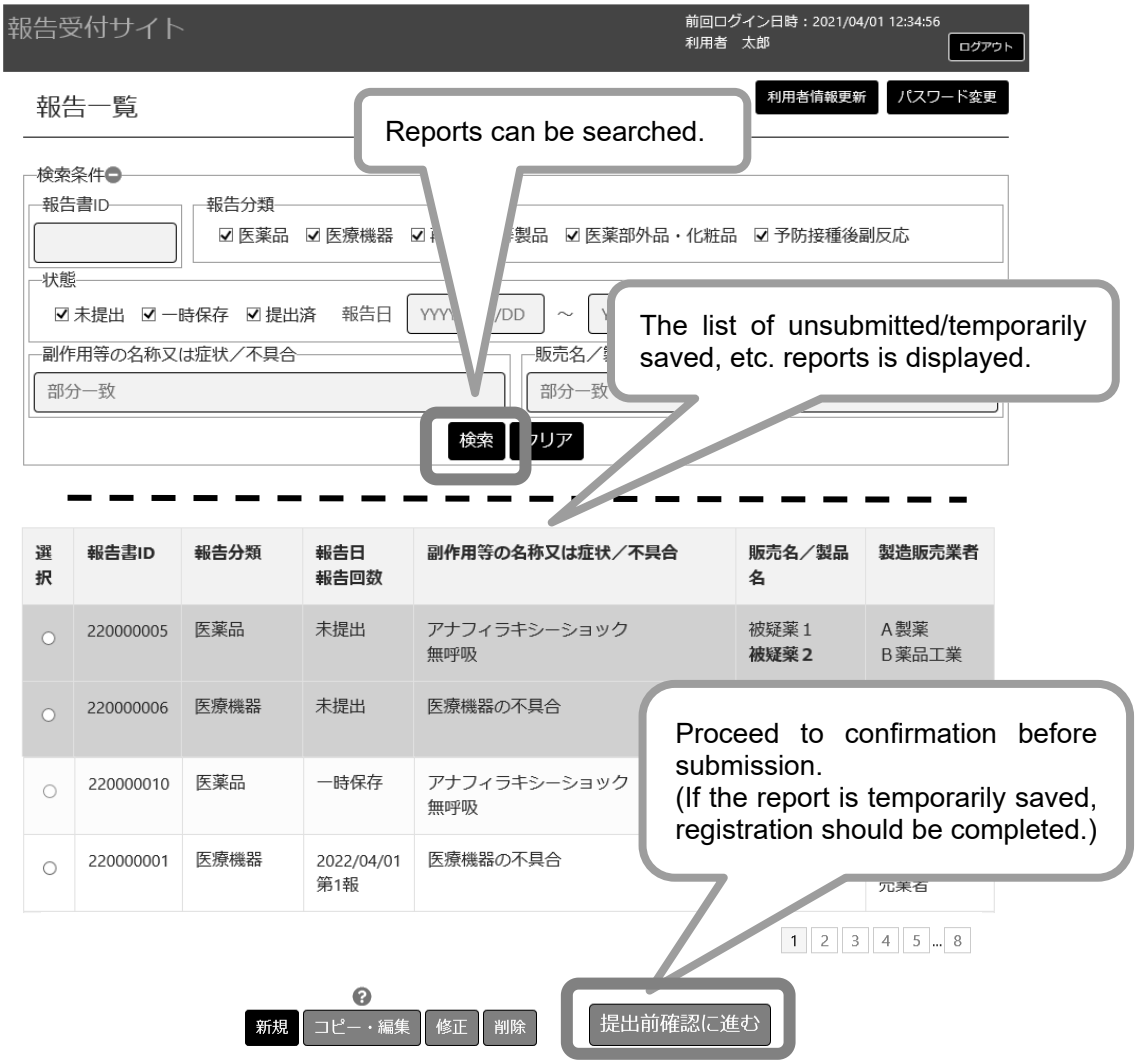
Each report form consists of multiple input screens such as "Drug type" and "Adverse drug reaction, etc.," which are displayed with tabs by color. After inputting data up to the last screen and pressing the "Register" button, the entries will be checked.

An error message will be displayed in red if there are any deficiencies in the entries. Please check the data that need corrections, etc.

< Report list screen >

On the report list screen, unsubmitted, temporarily saved, and submitted reports are displayed by color, and the list can be managed. Reports can also be searched.

Please note that a report cannot be submitted while it is temporarily saved. Resume data input by pressing the "Correction" button on the report list screen, and press "Proceed to confirmation before submission" on the report list screen after completion of report registration.



5. Request for Cooperation in Reporting

Reports on pharmaceuticals and medical devices safety information and reports on post-vaccination suspected adverse reactions from medical professionals are used for various safety measures such as revision of precautions.

Utilization of the Report Reception Site and continued cooperation in reporting from medical professionals would be very much appreciated.

[References]

・Adverse Reactions, Infections, Malfunctions Report pursuant to the Pharmaceuticals and Medical Devices Act (intended for healthcare professionals)
https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html (only in Japanese)

・Suspected Adverse Reactions Report pursuant to the Immunization Act (intended for healthcare professionals)
https://www.pmda.go.jp/safety/reports/hcp/prev-vacc-act/0003.html (only in Japanese)

・Report Reception Site
https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)

The Report Reception Site can be accessed by reading the QR code here.

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated March 15, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Nintedanib ethanesulfonate

Brand name (name of company)	Ofev Capsules 100 mg, 150 mg (Boehringer Ingelheim Japan, Inc.)
Therapeutic category	Agents affecting metabolism, n.e.c. (not elsewhere classified)
Indications	Idiopathic pulmonary fibrosis Systemic sclerosis-associated interstitial lung disease Progressive fibrosing interstitial lung disease

PRECAUTIONS (revised language is underlined)

[Under new instructions]

8. IMPORTANT PRECAUTIONS	Nephrotic syndrome may occur. Urine protein tests should be performed periodically during administration of this drug.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Nephrotic syndrome
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period (April 2018 to March 2021) Cases involving nephrotic syndrome: 6 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 12 683 Japanese market launch: August 2015

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 60s	Idiopathic pulmonary fibrosis (Proteinuria, lower limb oedema)	300 mg Approx. 11 months	**Thrombotic microangiopathy** Smoking history: 50 cigarettes per day, 48 years Partial lung resection was performed for tumor removal.	
				Day 1 of administration	Administration of nintedanib ethanesulfonate was initiated.
				1 week after administration	Nausea and diarrhea were noted and were controlled by symptomatic treatment. The dose of eplerenone was increased from 50 mg/day to 100 mg/day due to increased blood pressure.
				10 months after administration	The patient was admitted to the hospital for renal biopsy. Mottled tubular atrophy and interstitial enlargement were observed, but renal tubulitis was not. There were 21 glomeruli, one of which was totally sclerotic, and the others presented mild glomerular interstitial proliferation and extensively elongated subendothelial areas occupied by hyaline-like material accompanied by massive subendothelial deposits. Some of the subendothelial deposits were positive for periodic acid-Schiff (PAS) staining, but the others were negative. Localized mesangiolysis and double contour lines in some glomeruli were observed. An immunofluorescence staining test identified only moderate IgM deposits in the massive subendothelial deposits that were not positive in other staining tests. Electron microscopy showed high electron density deposits (EDDs) in the subendothelial and glomerular interstitial areas, but no foot-process effacement. A histological diagnosis revealed glomerular microangiopathy accompanied by subendothelial deposits.
				Day of discontinuation (11 months after administration)	Nephrotic syndrome was suspected, and administration of nintedanib ethanesulfonate was discontinued. Furosemide (20 mg/day) and trichlormethiazide (1 mg/day) were administered for nephrotic syndrome.
				1 month after discontinuation	Haematuria improved.
				3 months after discontinuation	Proteinuria gradually improved. Serum albumin increased to 3.4 g/dL. Oedema and hypertension improved. Furosemide, trichlormethiazide and amlodipine were discontinued. Eplerenone was decreased to 25 mg/day.
				4 months after discontinuation	Protein urine decreased to 0.3 g/gCr.

Laboratory test value

	4 months before administration	1 week after administration	10 months after administration
Serum creatinine (mg/dL)	0.78	NA	0.8
Serum albumin (g/dL)	NA	NA	2.5
Urinary protein/urine creatinine ratio (g/gCr)	NA	NA	4.1
Proteinuria (urine test paper)	(-)	2+	4+
Haematuria (urine test paper)	(-)	1+	2+

Concomitant drugs: Eplerenone, amlodipine

4
Revision of Precautions (No.331)

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 March 15, 2022.

1 Agents relating to blood and body fluids, n.e.c. (not elsewhere classified)
Ticagrelor

Brand name	Brilinta tablets 60 mg, 90 mg (AstraZeneca K.K.)
[Under New instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Bradyarrhythmia such as sinus arrest and an advanced type of atrioventricular block

2 Agents affecting metabolism, n.e.c. (not elsewhere classified)
Nintedanib ethanesulfonate

Brand name	Ofev Capsules 100 mg, 150 mg (Boehringer Ingelheim Japan, Inc.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Nephrotic syndrome may occur. Urine protein tests should be performed periodically during administration of this drug.
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Nephrotic syndrome

3 Anti-virus agents
Efavirenz

Brand name	Stocrin Tablets 200 mg, 600 mg (MSD K.K.)
[Under Old instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Psychoneurotic symptoms Ataxia, encephalopathy, coma, confusion, psychomotor slowing, psychosis, delirium, convulsions, epileptic seizures, etc. may occur. Cases of these symptoms that developed several months to several years following initiation of this drug have been reported.

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 28 February 2022)
◎: Products for which EPPV was initiated after February 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 5 to 11 years old	Pfizer Japan Inc.	February 22, 2022
◎	Selpercatinib[*1] Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	February 25, 2022
◎	Pegfilgrastim (genetical recombination)[*2] G-Lasta Subcutaneous Injection 3.6 mg	Kyowa Kirin Co., Ltd.	February 25, 2022
◎	Nirmatrelvir/ritonavir Paxlovid Pack	Pfizer Japan Inc.	February 14, 2022
	Tocilizumab (genetical recombination) [*3] Actemra for Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	January 21, 2022
	3-Iodobenzylguanidine (^{131}I) Raiatt MIBG-I 131 Injection	FUJIFILM Toyama Chemical Co., Ltd.	January 18, 2022
	Molnupiravir Lagevrio Capsules 200 mg	MSD K.K.	December 24, 2021
	Prasugrel hydrochloride[*4] Efient Tablets 2.5 mg, 3.75 mg	Daiichi Sankyo Co., Ltd.	December 24, 2021
	Azilsartan Azilva Granules 1%, Azilva Tablets 10 mg, 20 mg, 40 mg	Takeda Pharmaceutical Company Limited.	December 16, 2021
	Abrocitinib Cibinqo Tablets 50 mg, 100 mg, 200 mg	Pfizer Japan Inc.	December 13, 2021
	Selpercatinib Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	December 13, 2021

Nonproprietary name Brand name		Name of the MAH	Date of EPPV initiate
	Somapacitan (genetical recombination) Sogroya Subcutaneous Injection 5 mg, 10 mg	Novo Nordisk Pharma Ltd.	December 10, 2021
	Enfortumab vedotin (genetical recombination) Padcev for I.V. infusion 30 mg	Astellas Pharma Inc.	November 30, 2021
	Progesterone F-meno capsules 100 mg	Fuji Pharma Co., Ltd.	November 29, 2021
	Avalglucosidase alfa (genetical recombination) Nexviazyme for I.V. Infusion 100 mg	Sanofi K.K.	November 26, 2021
	Tucidinostat[*5] Hiyasta tablets 10 mg	Huya Japan G.K.	November 25, 2021
	Empagliflozin[*6] Jardiance Tablets 10 mg	Boehringer Ingelheim Japan, Inc.	November 25, 2021
	Anifrolumab (genetical recombination) Saphnelo for I.V. infusion 300 mg	AstraZeneca K.K.	November 25, 2021
	Relebactam hydrate/imipenem hydrate/cilastatin sodium Recarbrio Combination for Intravenous Drip Infusion	MSD K.K.	November 9, 2021
	Casirivimab (genetical recombination), Imdevimab (genetical recombination) Ronapreve Injection Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	November 5, 2021
	Tucidinostat Hiyasta tablets 10 mg	Huya Japan G.K.	October 20, 2021
	Follitropin delta (genetical recombination) Rekovelle Pen for S.C. Injection 12 μg, 36 μg, 72 μg	Ferring Pharmaceuticals Co., Ltd.	October 1, 2021
	Sotrovimab (genetical recombination) Xevudy for Intravenous Injection 500 mg	GlaxoSmithKline K.K.	September 29, 2021
	L-Lysine hydrochloride, L-arginine hydrochloride Lysakare Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
	Lutetium (^{177}Lu) hepato Lutathera Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
	Midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	September 27, 2021
	Rituximab (genetical recombination)[*7] Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	September 27, 2021
	Sacubitril valsartan sodium hydrate[*8] Entresto Tablets 100 mg, 200 mg	Novartis Pharma K.K.	September 27, 2021
	Sirolimus[*9] Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	September 27, 2021

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	Ibrutinib*10 Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	September 27, 2021
	Secukinumab (genetical recombination) [1] Cosentyx for s.c. injection 150 mg syringe [2] Cosentyx for s.c. injection 150 mg pen [3] Cosentyx for s.c. injection 75 mg syringe	Novartis Pharma K.K.	September 27, 2021
	Dinutuximab (genetical recombination) Unituxin I.V. injection 17.5 mg/5 mL	Ohara Pharmaceutical Co., Ltd.	September 22, 2021
	Imeglimin hydrochloride Twymeeg Tablets 500 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 16 2021
	Vericiguat Verquvo tablets 2.5 mg, 5 mg, 10 mg	Bayer Yakuhin Ltd.	September 15, 2021

*1 Radically unresectable RET fusion-positive thyroid cancer, radically unresectable RET-mutant medullary thyroid cancer

*2 Mobilization of haematopoietic stem cells into peripheral blood for allogeneic blood stem cell transplantation

*3 SARS-CoV-2 pneumonia (limited to patients requiring oxygen intervention)

*4 Prevention of recurrence of ischaemic cerebrovascular disease following the former appearance of ischaemic cerebrovascular disease (associated with large-artery atherosclerosis or small-vessel occlusion) (restricted to cases with a high risk of ischaemic stroke).

*5 Relapsed or refractory peripheral T-cell lymphoma

*6 Chronic heart failure (only in patients who are receiving standard of care for chronic heart failure)

*7 Systemic scleroderma

*8 Hypertension

*9 Refractory lymphatic diseases (lymphangioma (lymphatic malformation), lymphangiomatosis, Gorham's disease, lymphangiectasia)

*10 Chronic graft versus host disease after haematopoietic stem cell transplantation (when steroids are not sufficiently effective)