Pharmaceuticals and Medical Devices Safety Information

No. 403 August 2023

Table of Contents

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

Published by
Ministry of Health, Labour and Welfare

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

This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 403 August 2023

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

[Outline of Information]

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

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

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

Please utilize the Report Reception Site for reporting.
(This service is available only in Japanese.)

https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
NDMA	N-nitrosodimethylamine
PMDA	Pharmaceuticals and Medical Devices Agency

1
Safety Measures Against the Risks of Contamination with Nitrosamines in Drugs

1. Introduction

In recent years, nitrosamines, such as N-nitrosodimethylamine (NDMA), which may have carcinogenic risks, have been detected in sartan drugs, ranitidine, nizatidine, metformin, etc. in Japan and overseas, and some products have been voluntarily recalled. Based on these cases, the MHLW is promoting efforts to reduce and control the contamination with nitrosamines in drugs. This article introduces the latest information.

2. Response to contamination with nitrosamines

In July 2018, NDMA was detected in the drug substance manufactured by Zhejiang Huahai Pharmaceutical Co., Ltd., and it was announced that the drug product using the drug substance in question would be recalled throughout Europe. Thereafter, contamination with nitrosamines for the following drugs has also been reported in Japan: Sartan drugs, ranitidine, nizatidine, and metformin. Since it is important to reduce the risk of contamination with nitrosamines as much as possible, on October 8, 2021, the MHLW notified prefectural governments in Japan to instruct the marketing authorization holders (MAHs) under jurisdiction to perform self-inspection on the risk of contamination with nitrosamines. Mainly, the following three measures are to be taken in self-inspection of drugs already on the market.

(1) The risk of contamination with nitrosamines shall be evaluated by April 30, 2023, in consideration of the manufacturing method, etc. with reference to the known causes of contamination with nitrosamines.
(2) For products that have a risk of contamination with nitrosamines, the amount of nitrosamines that may be contained in the drugs concerned shall be measured using an appropriate number of lots.
(3) As a result of (2) above, products that are found to be contaminated with nitrosamines exceeding the acceptable limit shall be promptly reported to the MHLW, and risk mitigation measures such as setting specifications and changing the manufacturing method to reduce the amount of nitrosamines shall be implemented by October 31, 2024. (If an application for approval of partial change or a notification of minor change is required, such an application or notification shall be made by October 31, 2024.)

In the presence of secondary or tertiary amines, nitrosamines may be formed by the reaction with compounds with nitrosation potential such as sodium nitrite ($NaNO_2$). Contamination with nitrosamines is known to be caused by various reasons, such as generation in the manufacturing process, contamination from raw materials, etc., and generation during storage. However, the cause of the contamination may not be identified immediately at the time of detecting the contamination, and a certain period of time is required before establishing risk mitigation measures by setting specifications or changing manufacturing methods.

3. Risk assessment of contamination with nitrosamines

Assessment of impurities with a carcinogenic risk in drugs is generally based on whether it exceeds the carcinogenic risk ("approximately 1 additional cancer per 100 000 persons" over a lifetime of exposure), which is considered to be acceptable in international guidelines ("Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (ICH-M7 Guidelines)).

For this risk assessment, data, etc. from toxicity studies in which carcinogenicity was investigated by administering the impurity to animals are used. However, contamination with

nitrosamines for which toxicity study data are not available has recently been reported. In this case, while the carcinogenicity of the nitrosamines concerned in animals is unknown, a provisional risk assessment has been performed using the toxicity data of compounds with a similar chemical structure, etc. To elucidate the carcinogenicity of these nitrosamines, it is generally confirmed whether they have carcinogenicity caused by genotoxicity in studies to detect mutation using bacteria and gene mutation studies in transgenic animals. If carcinogenicity is not ruled out, carcinogenicity studies in animals will be considered to clarify the strength of carcinogenicity. This carcinogenicity study requires a period of several years.

If the risk assessment based on the toxicity study data or provisional risk assessment reveals the presence of nitrosamines exceeding the acceptable limit in terms of the carcinogenic risk, the MAHs, etc. are required to inform healthcare professionals of the fact. In recent cases, contamination with N-nitrosonortriptyline, a compound classified as a nitrosamine, has been found in nortriptyline products. On the supposition that N-nitrosonortriptyline is carcinogenic, the level of increase in the risk of developing cancer was found to be greater than the risk of "approximately 1 additional cancer per 100 000 persons."[1] Since nortriptyline is a tricyclic antidepressant, patients may experience withdrawal symptoms, etc. by rapid dose reduction or discontinuation of the drug. Therefore, patients need to be informed that they should not stop taking the drug without consulting a physician. In addition, physicians or pharmacists are requested to explain other treatment options as well as the level of the risks to patients currently taking the drug.

4. Conclusion

For nitrosamines that may have carcinogenic risk, reducing the risk of contamination as much as possible is a very important issue. The MHLW cooperates with foreign regulatory authorities, etc. to continuously implement and review necessary measures to deal with the contamination with nitrosamines, etc. Even if contamination of nitrosamines exceeding the risk of "approximately 1 additional cancer per 100 000 persons" is detected, we consider that it is generally important that patients do not stop taking the drug without consulting a physician, and healthcare professionals are encouraged to communicate with patients for proper use of drugs based on the information provided for each drug.

[Reference]

For information on the risks of contamination with nitrosamines in drugs to date, please refer to the following webpages of the PMDA.

○ Measures against the risk of contamination with nitrosamines in drugs
https://www.pmda.go.jp/safety/info-services/drugs/0371.html (only in Japanese)

Information on individual drugs and other details are available at the following.

○ Administrative notices concerning individual drugs related to contamination with nitrosamines
Measures for the Detection of Nitrosamines From Nortriptyline Hydrochloride Products
https://www.pmda.go.jp/files/000252879.pdf (only in Japanese)
Results of the Health Effect Assessment of the Use of Amoxapine Products in Which N-nitroso-amoxapine Was Detected

[1] The European Medicines Agency (EMA) has published an acceptable daily intake for N-nitrosonortriptyline based on the toxicity data for compounds with a chemical structure similar to that of N-nitrosonortriptyline. As a result of consideration based on the toxicity data referred to by the EMA and the level of N-nitrosonortriptyline detected in the products distributed in Japan, assuming that 150 mg of this drug is taken every day and the duration of use does not usually exceed 10 years, the level of increase in the theoretical carcinogenic risk is evaluated to be equivalent to an excess risk of approximately 1 in 23 000 persons developing cancer in their lifetime. The details of the calculation method are shown in "Measures for the Detection of Nitrosamines From Nortriptyline Hydrochloride Products" (Joint Administrative Notice issued by Pharmaceutical Safety Division and Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 8, 2023).

https://www.pmda.go.jp/files/000248844.pdf (only in Japanese)
Measures for the Detection of Nitrosamines From Sitagliptin Phosphate Hydrate Products
https://www.pmda.go.jp/files/000248055.pdf (only in Japanese)
Results of the Health Effect Assessment of the Use of Metformin Products in Which N-nitrosodimethylamine Was Detected
https://www.pmda.go.jp/files/000237205.pdf (only in Japanese)
Results of the Health Effect Assessment of the Use of Ranitidine Hydrochloride Products or Nizatidine Products in Which N-dimethylnitrosamine Was Detected
https://www.pmda.go.jp/files/000236355.pdf (in Japanese)
English translation by the PMDA
https://www.pmda.go.jp/files/000237223.pdf
Results of Deliberation of the FY 2018 Subcommittee on Drug Safety of the Committee on Drug Safety (the 8th meeting) on the Detection of Carcinogenic Substances From Valsartan Preparations
https://www.pmda.go.jp/files/000226196.pdf (only in Japanese)

○ Notifications and administrative notices related to self-inspection
Self-inspection on Risks of Contamination With Nitrosamines in Drugs
https://www.pmda.go.jp/files/000243028.pdf (in Japanese)
English translation by the PMDA
https://www.pmda.go.jp/files/000243438.pdf
Questions and Answers (Qs & As) on "Self-inspection on Risks of Contamination With Nitrosamines in Drugs"
https://www.pmda.go.jp/files/000249536.pdf (only in Japanese)

○ Materials of the Subcommittee on Drug Safety of the Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council
The FY 2023 Subcommittee on Drug Safety of the Committee on Drug Safety (the 3rd meeting) (Materials 2-1 to 2-2)
https://www.mhlw.go.jp/stf/newpage_33471.html (only in Japanese)
The FY 2022 Subcommittee on Drug Safety of the Committee on Drug Safety (the 17th meeting) (Materials 1-1 to 1-3)
https://www.mhlw.go.jp/stf/newpage_28762.html (only in Japanese)
The FY 2020 Subcommittee on Drug Safety of the Committee on Drug Safety (the 7th meeting) (Material 2)
https://www.mhlw.go.jp/stf/newpage_13767.html (only in Japanese)
The FY 2018 Subcommittee on Drug Safety of the Committee on Drug Safety (the 9th meeting) (Material 3-1)
https://www.mhlw.go.jp/stf/shingi2/0000183979_00001.html (only in Japanese)
The FY 2018 Subcommittee on Drug Safety of the Committee on Drug Safety (the 8th meeting) (Materials 2-1 to 2-5 and others)
https://www.mhlw.go.jp/stf/shingi2/0000206683_00001.html (only in Japanese)

2

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated July 20, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 1. [1] Atorvastatin calcium hydrate, [2] Simvastatin, [3] Pitavastatin calcium hydrate, [4] Pravastatin sodium, [5] Fluvastatin sodium, [6] Rosuvastatin calcium, [7] Amlodipine besilate/atorvastatin calcium hydrate, [8] Ezetimibe/atorvastatin calcium hydrate, [9] Ezetimibe/rosuvastatin calcium, [10] Pitavastatin calcium hydrate/ezetimibe

Brand name (name of company)	[1] Lipitor Tablets 5 mg, 10 mg (Viatris Pharmaceuticals Japan Inc.), and the others [2] Lipovas Tablets 5, 10, 20 (Organon K.K.), and the others [3] Livalo Tablets 1 mg, 2 mg, 4 mg, Livalo OD Tablets 1 mg, 2 mg, 4 mg (Kowa Company, Ltd.), and the others [4] Mevalotin Tablets 5, 10, Mevalotin Fine Granules 0.5%, 1% (Daiichi Sankyo Co., Ltd.), and the others [5] Lochol Tablets 10 mg, 20 mg, 30 mg (Sun Pharma Japan Limited), and the others [6] Crestor Tablets 2.5 mg, 5 mg, Crestor OD Tablets 2.5 mg, 5 mg (AstraZeneca K.K.), and the others [7] Caduet Combination Tablets 1 ban, 2 ban, 3 ban, 4 ban (Viatris Pharmaceuticals Japan Inc.), and the others [8] Atozet Combination Tablets LD, HD (Organon K.K.), and the others [9]Rosuzet Combination Tablets LD, HD (Organon K.K.) [10]Livazebe Combination Tablets LD, HD (Kowa Company, Ltd.)
Therapeutic category	Agents for hyperlipidemias, other cardiovascular agents
Indications	[1], [3], [5], [6], [8] to [10] Hypercholesterolaemia, familial hypercholesterolaemia [2], [4] Hyperlipidaemia, familial hypercholesterolaemia [7] This drug (amlodipine/atorvastatin combination drug) should be used in the following patients for whom treatment with both amlodipine and atorvastatin is appropriate: Patients with hypertension or angina pectoris, hypercholesterolaemia or familial hypercholesterolaemia The indications for amlodipine and atorvastatin are as follows: Amlodipine •Hypertension •Angina pectoris Atorvastatin •Hypercholesterolaemia •Familial hypercholesterolaemia

PRECAUTIONS (Revised language is underlined.)

[Under old instructions]	
[Careful Administration] (newly added)	Patients with myasthenia gravis or a history of it [Exacerbation or relapse of myasthenia gravis (ocular or systemic) may occur.]
[Adverse Reactions Clinically Significant Adverse Reactions] (newly added)	Myasthenia gravis: Myasthenia gravis (ocular or systemic) may occur or worsen. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with myasthenia gravis or a history of it Exacerbation or relapse of myasthenia gravis (ocular or systemic) may occur.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Myasthenia gravis Myasthenia gravis (ocular or systemic) may occur or worsen.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports <Myasthenia gravis> [1] One case has been reported to date. (No patient mortalities) [2] to [10] No cases have been reported to date. <Ocular myasthenia> No cases have been reported to date for [1] to [10]. Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 788 648 Descriptions are omitted hereinafter because there are many relevant drug products. Japanese market launch: [1] May 2000 Descriptions are omitted hereinafter because there are many relevant drug products.

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/ age</th><th>Reason for use (complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Female 60s</td><td>Unknown (myasthenia gravis, ocular myasthenia)</td><td>Unknown</td><td>Exacerbation of myasthenia gravis
4 years before administration: The patient was diagnosed with ocular myasthenia.
Date unknown: The patient discontinued taking pyridostigmine bromide for 18 months since her condition improved with the drug.
Start of administration: Oral administration of atorvastatin calcium hydrate was initiated.
Week 4 of administration: Symptoms of diplopia and eyelid ptosis recurred.
The patient was negative for anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies.
The quantitative myasthenia gravis (MG) score increased to 8 following an elevation of anti-acetylcholine receptor antibody titers.
Administration of atorvastatin calcium hydrate was discontinued. Pyridostigmine bromide was resumed.
Date unknown: Since pyridostigmine bromide was not effective, administration of prednisolone (10 mg/day) was initiated.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table>
<tr><th></th><th>4 years before administration</th><th>2 years before administration</th><th>Week 4 of administration</th><th>2 years after discontinuation</th></tr>
<tr><td>Anti-AChR (nM)</td><td>18</td><td>9.8</td><td>32</td><td>19</td></tr>
<tr><td>Anti-HMGCR</td><td>(−)</td><td>−</td><td>(−)</td><td>−</td></tr>
<tr><td>QMG score</td><td>7</td><td>2</td><td>8</td><td>3</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Suspected concomitant drugs: None
Concomitant drugs: None</td></tr>
</table>

3
Revision of PRECAUTIONS (No.343)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated July 20, 2023.

1 Agents for hyperlipidemias, other cardiovascular agents

[1] Atorvastatin calcium hydrate
[2] Ezetimibe/atorvastatin calcium hydrate
[3] Ezetimibe/rosuvastatin calcium
[4] Simvastatin
[5] Pitavastatin calcium hydrate
[6] Pitavastatin calcium hydrate/ezetimibe
[7] Pravastatin sodium
[8] Fluvastatin sodium
[9] Rosuvastatin calcium
[10] Amlodipine besilate/atorvastatin calcium hydrate

Brand name	[1] Lipitor Tablets 5 mg, 10 mg (Viatris Pharmaceuticals Japan Inc.), and the others [2] Atozet Combination Tablets LD, HD (Organon K.K.), and the others [3] Rosuzet Combination Tablets LD, HD (Organon K.K.) [4] Lipovas Tablets 5, 10, 20 (Organon K.K.), and the others [5] Livalo Tablets 1 mg, 2 mg, 4 mg, Livalo OD Tablets 1 mg, 2 mg, 4 mg (Kowa Company, Ltd.), and the others [6] Livazebe Combination Tablets LD, HD (Kowa Company, Ltd.) [7] Mevalotin Tablets 5, 10, Mevalotin Fine Granules 0.5%, 1% (Daiichi Sankyo Co., Ltd.), and the others [8] Lochol Tablets 10 mg, 20 mg, 30 mg (Sun Pharma Japan Limited), and the others [9] Crestor Tablets 2.5 mg, 5 mg, Crestor OD Tablets 2.5 mg, 5 mg (AstraZeneca K.K.), and the others [10] Caduet Combination Tablets 1 ban, 2 ban, 3 ban, 4 ban (Viatris Pharmaceuticals Japan Inc.), and the others
[Under old instructions]	
Careful Administration (newly added)	Patients with myasthenia gravis or a history of it [Exacerbation or relapse of myasthenia gravis (ocular or systemic) may occur.]
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Myasthenia gravis: Myasthenia gravis (ocular or systemic) may occur or worsen. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	Patients with myasthenia gravis or a history of it Exacerbation or relapse of myasthenia gravis (ocular or systemic) may occur.

9.1 Patients with Complication or History of Diseases, etc. (newly added)	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Myasthenia gravis Myasthenia gravis (ocular or systemic) may occur or worsen.

2 Other hormone preparations

Tirzepatide

Brand name	Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos (Eli Lilly Japan K.K.)
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Anaphylaxis, angioedema

3 Antibiotic preparations acting mainly on gram-positive, gram-negative bacteria, and rickettsia and chlamydia

Minocycline hydrochloride (oral dosage form, injections)

Brand name	Minomycin Granules 2%, Minomycin Tablets 50 mg, Minomycin Capsules 50 mg, 100 mg, Minomycin Intravenous 100 mg (For Drip Use) (Pfizer Japan Inc.), and the others
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions	Lupus-like syndrome: Lupus-like syndrome may occur. If these symptoms occur, administration of this drug should be discontinued, and appropriate measures should be taken. Cases have been reported more frequently, especially in long-term treatment cases where this drug has been used for more than 6 months.
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions	Lupus-like syndrome Cases have been reported more frequently, especially in long-term treatment cases where this drug has been used for more than 6 months.

4 Anti-virus agents

Ensitrelvir fumaric acid

Brand name	Xocova Tablets 125 mg (Shionogi & Co., Ltd.)
[Under new instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Anaphylaxis

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 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 June 30, 2023)
◎: Products for which EPPV was initiated after June 1, 2023

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) [*1] Vaxneuvance Aqueous Suspension Syringes	MSD K.K.	June 26, 2023
◎	Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg	Teijin Pharma Limited.	June 26, 2023
◎	Somapacitan (genetical recombination) [*2] Sogroya Subcutaneous Injection 5 mg, 10 mg, 15 mg	Novo Nordisk Pharma Ltd.	June 26, 2023
◎	Mirikizumab (genetical recombination) [1] Omvoh Intravenous Infusion 300 mg [2] Omvoh Subcutaneous Injection 100 mg Autoinjectors [3] Omvoh Subcutaneous Injection 100 mg Syringes	Eli Lilly Japan K.K.	June 21, 2023
◎	Cholic acid Orphacol Capsules 50 mg	ReqMed Company, Ltd.	June 19, 2023
◎	Vedolizumab (genetical recombination) Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg	Takeda Pharmaceutical Company Limited.	June 19, 2023
◎	Crisantaspase Erwinase for intramuscular injection 10000	Ohara Pharmaceutical Co., Ltd.	June 14, 2023
◎	Tirzepatide Mounjaro Subcutaneous Injection Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos	Eli Lilly Japan K.K.	June 12, 2023
◎	Ropeginterferon alfa-2b (genetical recombination)	PharmaEssentia Japan	June 1,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Besremi Subcutaneous Injection Syringes 250 μg, 500 μg	KK	2023
◎	Oxybutynin hydrochloride[*3] Apohide Lotion 20%	Hisamitsu Pharmaceutical Co., Inc.	June 1, 2023
◎	Avatrombopag maleate Doptelet tablets 20 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	June 1, 2023
	Pegvaliase (genetical recombination) Palynziq Subcutaneous Injection 2.5 mg, 10 mg, 20 mg	BioMarin Pharmaceutical Japan K.K.	May 24, 2023
	Mifepristone/misoprostol Mefeego Pack	Linepharma KK	May 16, 2023
	Treprostinil Treprost Inhalation Solution 1.74 mg	Mochida Pharmaceutical Co., Ltd.	May 16, 2023
	Tirzepatide Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos	Eli Lilly Japan K.K.	April 18, 2023
	Edaravone Radicut Ors 2.1%	Mitsubishi Tanabe Pharma Corporation	April 17, 2023
	Donepezil Allydone Patches 27.5 mg, 55 mg	Teikoku Seiyaku Co., Ltd.	April 14, 2023
	Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) Vaxneuvance Aqueous Suspension Syringes	MSD K.K.	April 10, 2023
	Isavuconazonium sulfate Cresemba Capsules 100 mg, Cresemba for i.v. infusion 200 mg	Asahi Kasei Pharma Corporation	April 6, 2023
	Fostamatinib sodium hydrate Tavalisse Tablets 100 mg, 150 mg	Kissei Pharmaceutical Co., Ltd.	April 6, 2023
	Cemiplimab (genetical recombination) Libtayo I.V. Infusion 350 mg	Sanofi K.K.	March 30, 2023
	Tremelimumab (genetical recombination) Imjudo Injection 25 mg, 300 mg	AstraZeneca K.K.	March 15, 2023
	Ferric derisomaltose MonoVer for I.V. Injection 500 mg, 1000 mg	Nippon Shinyaku Co., Ltd.	March 15, 2023
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)[*4] Comirnaty intramuscular injection for 5 to 11 years old (Bivalent: Original/Omicron BA.4-5)	Pfizer Japan Inc.	March 3, 2023
	Dexmedetomidine hydrochloride[*5] Precedex Injections Solution 200 μg [Pfizer],	Pfizer Japan Inc.	February 24, 2023

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	200 μg/50 mL syringe [Pfizer]		
	Risankizumab (genetical recombination)*6 Skyrizi Auto dosers 360 mg	AbbVie GK	February 13, 2023
	Meningococcal polysaccharide-tetanus toxoid conjugate (serogroups A, C, W, and Y) MenQuadfi intramuscular injection	Sanofi K.K.	February 10, 2023
	Abaloparatide acetate Ostabalo Subcutaneous Injection Cart 1.5 mg	Teijin Pharma Limited.	January 30, 2023
	Risankizumab (genetical recombination) Skyrizi Intravenous infusion 600 mg	AbbVie GK	January 13, 2023

*1 Prevention of invasive disease caused by *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in children

*2 Growth hormone-deficient short stature without epiphyseal closure

*3 Primary palmar hyperhidrosis

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

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

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