Pharmaceuticals and Medical Devices Safety Information

No. 400 April 2023

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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.

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Pharmaceuticals and Medical Devices Safety Information

No. 400 April 2023

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

[Outline of Information]

No.	Subject	Measures	Outline of Information	Page
1	**Revision of Drugs That May Cause Abuse, Etc.**		The Minister of Health, Labour and Welfare designates drugs that may cause abuse, etc. among over-the-counter (OTC) drugs, etc. as "Drugs Designated by the Minister of Health, Labour and Welfare as Drugs That May Cause Abuse, Etc. Under the Provisions of Article 15-2 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Public Notice of Ministry of Health, Labour and Welfare No. 252 of 2014) pursuant to the provisions of Article 15-2 of the "Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Ministry of Health and Welfare Ordinance No. 1 of 1961). This time, the target has been amended in accordance with "Partial Revision of Drugs Designated by the Minister of Health, Labour and Welfare as Drugs That May Cause Abuse, Etc. Under the Provisions of Article 15-2 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Public Notice of Ministry of Health, Labour and Welfare No. 5 of 2023), and it has been decided that it will be implemented from April 1, 2023. The background is explained in this section.	5
2	**Revision of Precautions for Antitubercular Agents**	*P*	Paradoxical drug reactions have long been known. The Ministry of Health, Labour and Welfare (MHLW) issued a notification that instructs the revision of Precautions for all the antitubercular agents on March 23, 2023 in view of the current situation of clinical practice, etc. in the treatment for tuberculosis. Therefore, this section introduces the background of the discussion on the instruction of the revision.	8
3	**Important Safety Information**	*P* *C*	Borofalan (^{10}B) Regarding the revision of the Precautions of drugs in accordance with the Notification dated March 23, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.	10
4	**Revision of Precautions (No. 340)**	*P*	Borofalan (^{10}B) (and 6 others)	12
5	**List of Products Subject to Early Post-marketing Phase Vigilance**		List of products subject to Early Post-marketing Phase Vigilance as of February 28, 2023	15
	(Reference) Terminology of		In principle, "phaeochromocytoma" should be changed to "phaeochromocytoma or	18

	“Phaeochromocytoma” in the Precautions of Drugs (Excluding *in vitro* Diagnostics)		paraganglioma" for drug products for which attention is called for as "phaeochromocytoma" in the Precautions of electronic package inserts. This section introduces details of the change.	

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
HSB	Health Service Bureau
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
OTC	Over-the-Counter
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
TIDCD	Tuberculosis and Infectious Diseases Control Division

1
Revision of Drugs That May Cause Abuse, Etc.

The Minister of Health, Labour and Welfare designates drugs that may cause abuse, etc. among over-the-counter (OTC) drugs, etc. as "Drugs Designated by the Minister of Health, Labour and Welfare as Drugs That May Cause Abuse, Etc. Under the Provisions of Article 15-2 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Public Notice of Ministry of Health, Labour and Welfare No. 252 of 2014) pursuant to the provisions of Article 15-2 of the "Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Ministry of Health and Welfare Ordinance No. 1 of 1961).

This time, the target has been amended as shown in the table below in accordance with "Partial Revision of Drugs Designated by the Minister of Health, Labour and Welfare as Drugs That May Cause Abuse, Etc. Under the Provisions of Article 15-2 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Public Notice of Ministry of Health, Labour and Welfare No. 5 of 2023), and it has been decided that it will be implemented from April 1, 2023. The background is explained below.

After revision	Before revision
1. Ephedrine	1. Ephedrine
2. Codeine	2. Codeine (limited to antitussive and expectorant drugs.)
3. Dihydrocodeine	3. Dihydrocodeine (limited to antitussive and expectorant drugs.)
4. Bromovalerylurea	4. Bromovalerylurea
5. Pseudoephedrine	5. Pseudoephedrine
6. Methylephedrine	6. Methylephedrine (limited to oral solutions among antitussive and expectorant drugs.)

[Background]

In the review of the drug sales system pertinent to the revision of the Pharmaceutical Affairs Act in 2013, "drugs that may cause abuse, etc." were designated, and in addition to providing information according to risk category regarding the OTC drugs including these ingredients, the following measures are currently taken:

(1) Confirmation of the name and age when the purchaser is a young person;
(2) Confirmation of the purchase status at other stores, reason for purchase, etc.;
(3) Limitation of the quantity at the time of sale (in principle, one package per person).

In FY 2019 Health, Labour and Welfare Policy Research Grants (Health, Labour and Welfare Sciences Special Research Project) "Re-analysis and additional survey on the actual status of dependence in users of private dependence support groups" (Principal investigator: Takuya Shimane, Department of Drug Dependence Research, National Institute of Mental Health, National Center of Neurology and Psychiatry; hereinafter referred to as "FY 2019 Health, Labour and Welfare Policy Research Grants"), drug dependence associated with abuse of OTC drugs was reported. In addition, in order to comprehensively understand the recent status of abuse of OTC drugs, cases of intentional overdose of OTC drugs were collected and analyzed among the consultations held with the Japan Poison Information Center, which accepts telephone

consultations, etc. on acute poisoning. These are summarized below.

● FY 2019 Health, Labour and Welfare Policy Research Grants (Analysis on drug-dependent patients)

According to the survey conducted by FY 2019 Health, Labour and Welfare Policy Research Grants for the purpose of understanding the actual status of patients with dependence on OTC drugs in users of DARC*, cases of dependence on not only antitussive and expectorant drugs containing dihydrocodeine and/or methylephedrine but also combination cold remedies containing the same ingredients were reported as major dependence on OTC drugs. Antipyretic analgesics, which contained bromovalerylurea, were also reported.

In addition, this survey showed that the "accessibility" and "legality" of OTC drugs were considered to lead to a high rate of repeated use and that a "history of use of illicit drugs," such as cannabis, was characteristic to patients with dependence (Cannabis (61.9%), stimulants (52.4%)).

* Drug Addiction Rehabilitation Center, where drug-dependent patients, who share the same problem of drug-dependence, support each other and work toward recovery from drug dependence through their own programs with a focus on group meeting

● Analysis by Japan Poison Information Center (Analysis on acute poisoning)

In order to comprehensively understand the actual situation not limited to drug-dependent patients, the cases of intentional overdose of OTC drugs were tabulated and analyzed among consultations held with the Japan Poison Information Center from 2017 to 2021.

When classified by therapeutic category, cases for antipyretic analgesic (389 cases (33%)) were most common, but the number of cases was also high for common cold medicines (combination cold remedies) (210 cases (18%)) and antitussive and expectorant drugs (176 cases (15%)), which were considered as major OTC drugs on which patients were dependent in the FY 2019 Health, Labour and Welfare Policy Research Grants. These combination cold remedies included those containing dihydrocodeine and/or methylephedrine, of which only antitussive and expectorant drugs were designated as drugs that may cause abuse, etc. As for drug products containing methylephedrine, cases for antitussive and expectorant drugs and combination cold remedies with dosage forms other than oral solution were reported.

In light of this situation, a deliberation was made at the 7th FY 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council held on July 27, 2022[i], and it was approved to revise the range of drugs that may cause abuse, etc. as described above. Then, public comments were solicited from September 2 to October 1, and, based on these results, the contents of the revision were approved at the 3rd FY 2022 Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council held on December 1[ii].

[Related notifications, etc.]

The handling, etc. of the contents of this revision are shown in "Revision of 'Drugs Designated by the Minister of Health, Labour and Welfare as Drugs That May Cause Abuse, Etc. Under the Provisions of Article 15-2 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices'" (PSEHB Notification No. 0208-1 by the Director-General of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated February 8, 2023). Pharmacies and those involved in pharmaceutical sales are requested to continue to cooperate in raising awareness about proper sales and prevention of abuse, etc.

In addition, the following awareness poster has been created for the purpose of preventing abuse, etc. of OTC drugs. Please download this poster from the URL shown below and post it at a store, etc. and use it to provide appropriate information to purchasers.

<<URL of the poster>>
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000204128_00007.html

i Material for the 7th FY 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council:
https://www.mhlw.go.jp/stf/newpage_27051.html
ii Material for the 3rd FY 2022 Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council:
https://www.mhlw.go.jp/stf/newpage_29460.html

2
Revision of Precautions for Antitubercular Agents

1. Introduction

In response to the addition of a cautionary statement regarding a paradoxical drug reaction to the Prescribing Information for some of the antitubercular agents in the US, the necessity of revision of electronic package inserts in Japan was discussed.

As a result of the investigation, including consultation with expert advisors, the Ministry of Health, Labour and Welfare (MHLW) instructed the marketing authorization holders to revise the Precautions for all the antitubercular agents on March 23, 2023 in view of the current situation of clinical practice, etc. in the treatment for tuberculosis. This section introduces the background of the discussion and other information.

2. Paradoxical drug reactions

After initiating treatment for tuberculosis, the conditions may occur in which chest x-ray findings such as enlargement of the shadow, appearance of new shadows, appearance of pleural effusions, a swelling/enlargement, etc. of mediastinal or cervical lymph nodes are observed although tubercle bacillus in the sputum decreased or converted to negative.[i] The event is also called initial aggravation or paradoxical reaction,[i, ii] but it did not occur only at the beginning of the treatment in cases of adverse drug reactions reported in Japan. Therefore, it was decided to add a cautionary statement using the terminology “paradoxical drug reaction.”

The event is supposed to involve a local allergy to bacterial cells of large numbers of tubercle bacilli which are rapidly killed by intensified chemotherapy.[ii, iii] In cases where the above mentioned findings are observed after initiating treatment for tuberculosis, if the isolated tubercle bacillus is a sensitive bacterium and patients regularly take the drugs, discontinuation or change of chemotherapy is not necessary,[ii] and it is considered that the symptoms typically improve after 3 to 6 months by continuing the treatment for tuberculosis.[i]

3. Details of the review

As a result of evaluating cases of adverse drug reactions reports involving paradoxical drug reactions for antitubercular agents marketed in Japan, cases of worsening of existing tuberculosis or new onset of tuberculosis symptoms have been observed for some of the agents after initiating treatment. However, appropriate measures were taken as treatment for paradoxical drug reactions without delay in all the cases.

A paradoxical drug reaction during the treatment for tuberculosis is an event advocated as initial aggravation in the 1970s[iv] and has long been known in Japan. No specific problems were observed in treating the event in the evaluated cases of adverse reactions reported in Japan. As a result of consultation with expert advisors, the MHLW/PMDA concluded that it is necessary to add a cautionary statement regarding paradoxical drug reactions in the Precautions of electronic package inserts for all the antitubercular agents based on the following points:

- Since hospital beds for tuberculosis have been phased out or decreased gradually due to a low prevalence of tuberculosis[v] in recent years, it is expected that the number of healthcare professionals who have little experience in treating tuberculosis in Japan will increase.
- Following HSB/TIDCD Notification No.0301-1 dated March 1, 2018, it is expected that tuberculosis treatment will be provided also at medical institutions other than those designated for this disease.

- The mechanism of a paradoxical drug reaction is supposed to involve an allergy to a bacterial cell of tubercle bacillus. Therefore, the event is not an adverse drug reaction caused by the active ingredients of antitubercular agents, and worsening of existing symptoms or new onset of symptoms of tuberculosis as mentioned in 2. above may be observed during the treatment course of tuberculosis.

4. In conclusion

Healthcare professionals should determine whether to continue administration of antitubercular agents with consideration given to the possibility of occurrence of paradoxical drug reactions if worsening of existing symptoms or new onset of symptoms of tuberculosis as mentioned in 2. above is observed after initiating treatment. They are requested to reconfirm the details of the revisions and to continue cooperation for proper use of antitubercular agents.

[Reference Information]

- Food and Drug Administration Drug Safety-related Labeling Changes (SrLC): RIFATER (10/21/2021, SUPPL-20)
  https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1034 Accessed March 6, 2023
- Revision of Precautions (PSEHB/PSD Notification No. 0323-1 dated March 23, 2023)
  https://www.mhlw.go.jp/content/001077070.pdf (in Japanese)
  English translation by the PMDA (March 23, 2023)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html
- Handling of Clerical Work Based on the Provisions of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Disease, Etc. Related to “Response Policies Regarding Proposals, Etc. From Local Region in 2017” (HSB/TIDCD Notification No.0301-1 dated March 1, 2018)

<Reference Literature>

i Tuberculosis Terminology “Initial Aggravation” The Japanese Society for Tuberculosis (currently The Japanese Society for Tuberculosis and Nontuberculous Mycobacteriosis)
https://www.kekkaku.gr.jp/glossary/index.php (only in Japanese)

ii Basic Knowledge of Tuberculosis 5th Revised Edition III. Treatment for tuberculosis. The Committee of Education and Terminology, The Japanese Society for Tuberculosis and Nontuberculous Mycobacteriosis. Kekkaku. 2021; 96: 93-123.
https://www.kekkaku.gr.jp/books-basic/pdf/3.pdf (only in Japanese)

iii Tatsushi Ando et al.: Severe respiratory failure with pulmonary tuberculosis during initial phase of chemotherapy. Kekkaku. 1989; 64: 519-27.

iv Eiichi Uragami et al.: An intriguing finding observed in the intensive chemotherapy of pulmonary tuberculosis. The Japanese Journal of Chest Diseases. 1978; 37: 882-93.

v Guidelines for management of tuberculosis in the sickbed of an infectious disease and cooperation with regional medical care. The Expert Committee of the Japanese Society for Tuberculosis. Kekkaku. 2019; 94: 425-29.
https://www.kekkaku.gr.jp/pub/vol94%282019%29/vol94no7p425-429.pdf

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated March 23, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Borofalan (^{10}B)

Brand name (name of company)	Steboronine 9000 mg/300 mL for infusion (STELLA PHARMA CORPORATION)
Therapeutic category	Other antitumor agents
Indications	Unresectable, locally advanced or recurrent head and neck cancer

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Pharyngolaryngeal oedema Pharyngolaryngeal oedema may occur, resulting in airway stenosis and obstruction.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving pharyngolaryngeal oedema: 4 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: 142 Japanese Market launch: May 2020

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
administration
duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
60s</td><td>Unresectable, locally recurrent head and neck cancer (Meniere's disease)</td><td>23 700 mg
once</td><td>Pharyngeal oedema, airways obstruction
Primary disease: Unresectable, locally recurrent head and neck cancer (squamous cell carcinoma) (primary site: Hypopharynx, recurrence site: Lymph node in right cervical region, Stage: IV A, TNM classification: T0N3bM0)
Approximately 3 years ago: At the time of the first episode, the patient had been treated with cisplatin and x-ray irradiation, and he had undergone left-sided neck dissection.
Approximately 7 months ago: At the time of recurrence, the patient was treated with nivolumab.
29 days before administration: The final dose of paclitaxel and cetuximab was administered.
Day 1 of administration (last day of administration): The patient was treated with 23 700 mg of borofalan (^{10}B) (once). Boron neutron capture therapy (BNCT) was performed. He received hydration. Parotitis was noted.
1 day after administration (day of onset): Hyperamylasaemia, pharyngeal oedema, queasy, and impaired appetite were noted. Dexamethasone sodium phosphate and dexamethasone were administered.
2 days after administration: The patient recovered from queasy and impaired appetite.
3 days after administration: The patient recovered from pharyngeal oedema.
4 days after administration: Hyperamylasaemia was resolving, and the patient recovered from parotitis.
49 days after administration (day of onset): Dysphagia, airway stenosis, and aspiration pneumonia were noted. Nasogastric tube insertion and tracheostomy were performed.
98 days after administration: The patient did not recover from dysphagia, airway stenosis, and aspiration pneumonia.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table><tr><th></th><th>1 day before administration</th><th>1 day after administration</th><th>4 days after administration</th></tr><tr><td>Serum amylase (U/L)</td><td>66</td><td>1 728</td><td>184</td></tr></table></td></tr>
<tr><td></td><td colspan="4">Concomitant drugs: None</td></tr>
</table>

4
Revision of Precautions (No.340)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated March 23, March 27, 2023.

1 Other antitumor agents
Borofalan (^{10}B)

Brand name

Steboronine 9000 mg/300 mL for infusion (STELLA PHARMA CORPORATION)

[Under new instructions]

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

Pharyngolaryngeal oedema
Pharyngolaryngeal oedema may occur, resulting in airway stenosis and obstruction.

2 Antibiotic preparations acting mainly on acid-fast bacteria, anti-tuberculous agents
[1] Enviomycin sulfate
[2] Cycloserine
[3] Aluminoparaaminosalicylate calcium hydrate
[4] Isoniazid
[5] Isoniazid sodium methanesulfonate hydrate
[6] Ethionamide
[7] Calcium paraaminosalicylate hydrate
[8] Pyrazinamide
[9] Bedaquiline fumarate

Brand name

[1] Tuberactin Inj. 1 g (Asahi Kasei Pharma Corporation)
[2] Cycloserine Capsules 250 mg “Meiji” (Meiji Seika Pharma Co., Ltd.)
[3] Alumino Nippas Calcium Granules 99% (Mitsubishi Tanabe Pharma Corporation)
[4] Iscotin Powder, Iscotin Tablets 100 mg, Iscotin Injection 100 mg (Alfresa Pharma Corporation), Hydra Tablet “Otsuka” 50 mg (Otsuka Pharmaceutical Factory, Inc.)
[5] Neoiscotin Powder, Neoiscotin Tablets 100 mg (Alfresa Pharma Corporation)
[6] Tubermin Tablets 100 mg (Meiji Seika Pharma Co., Ltd.)
[7] Nippas Calcium Granules 100% (Mitsubishi Tanabe Pharma Corporation)
[8] Pyramide Powder (Alfresa Pharma Corporation)
[9] Sirturo Tablets 100 mg (Janssen Pharmaceutical K.K.)

[Under old instructions]

Important Precautions (newly added)

A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

3 Antibiotic preparations acting mainly on acid-fast bacteria

[1] Kanamycin sulfate
[2] Streptomycin sulfate

Brand name	[1] Kanamycin Sulfate Injection 1000 mg "Meiji" (Meiji Seika Pharma Co., Ltd.) [2] Streptomycin Sulfate 1 g "Meiji" for Injection (Meiji Seika Pharma Co., Ltd.)

[Under old instructions]

Important Precautions (newly added)	A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	<Pulmonary tuberculosis and other tuberculosis> A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

4 Antibiotic preparations acting mainly on acid-fast bacteria

Rifabutin

Brand name	Mycobutin Capsules 150 mg (Pfizer Japan Inc.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	<Tuberculosis> A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

5 Antibiotic preparations acting mainly on acid-fast bacteria, anti-tuberculous agents, synthetic antibacterials

[1] Rifampicin
[2] Ethambutol hydrochloride
[3] Levofloxacin hydrate (oral dosage form)

Brand name	[1] Rifadin Capsules 150 mg (Daiichi Sankyo Co., Ltd.), and the others [2] Esanbutol Tablets 125 mg, 250 mg (Sandoz K.K.), Ebutol Tablets 125 mg, 250 mg (Kaken Pharmaceutical Co., Ltd.) [3] Cravit Tablets 250 mg, 500 mg, Cravit Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others

[Under old instructions]

Important Precautions	A paradoxical drug reaction may be observed due to the treatment with

(newly added)	antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	<Pulmonary tuberculosis and other tuberculosis> A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

6 Anti-tuberculous agents

Delamanid

Brand name	Deltyba tablets 50 mg (Otsuka Pharmaceutical Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	A paradoxical drug reaction may be observed due to the treatment with antitubercular agents including this drug. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

7 Other biological preparations

Anti-human thymocyte immunoglobulin, rabbit

Brand name	Thymoglobuline I.V. Infusion 25 mg (Sanofi K.K.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	<Common to all indications> When retreatment with this drug for patients who have previously received this drug or other preparations of rabbit serum is absolutely necessary, even after considering possible treatments with anti-human thymocyte immunoglobulin preparations derived from other species, this drug should be carefully administered under sufficient monitoring by a physician with necessary measures taken prior to treatment, such as confirming whether patients have antibodies to this drug or preparing for emergency treatment measures.

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 February 28, 2023)
◎: Products for which EPPV was initiated after February 1, 2023

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Dexmedetomidine hydrochloride[*1] / Precedex Injections Solution 200 μg [Pfizer], 200 μg/50 mL syringe [Pfizer]	Pfizer Japan Inc.	February 24, 2023
◎	Risankizumab (genetical recombination)[*2] / Skyrizi Auto dosers 360 mg	AbbVie GK	February 13, 2023
◎	Meningococcal polysaccharide-tetanus toxoid conjugate (serogroups A, C, W, and Y) / MenQuadfi intramuscular injection	Sanofi K.K.	February 10, 2023
	Abaloparatide acetate / Ostabalo Subcutaneous Injection Cart 1.5 mg	Teijin Pharma Limited.	January 30, 2023
	Risankizumab (genetical recombination) / Skyrizi Intravenous infusion 600 mg	AbbVie GK	January 13, 2023
	Caplacizumab (genetical recombination) / Cablivi Injection 10 mg	Sanofi K.K.	December 23, 2022
	Valemetostat tosilate / Ezharmia Tablets 50 mg, 100 mg	Daiichi Sankyo Co., Ltd.	December 20, 2022
	Ozoralizumab (genetical recombination) / Nanozora 30 mg Syringes for S.C. Injection	Taisho Pharmaceutical Co., Ltd.	December 1, 2022
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) / Spikevax Intramuscular Injection (Bivalent: Original/Omicron BA.4-5)	Moderna Japan Co., Ltd.	November 28, 2022
	Ensitrelvir fumaric acid / Xocova Tablets 125 mg	Shionogi & Co., Ltd.	November 24, 2022
	Human C1-inactivator / Berinert S.C. Injection 2000	CSL Behring K.K.	November 21, 2022

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Vutrisiran sodium Amvuttra Subcutaneous Injection 25 mg Syringe	Alnylam Japan K.K.	November 18, 2022
Deucravacitinib Sotyktu tablets 6 mg	Bristol-Myers Squibb K.K.	November 16, 2022
Tezepelumab (genetical recombination) Tezspire Subcutaneous Injection 210 mg	AstraZeneca K.K.	November 16, 2022
Spesolimab (genetical recombination) Spevigo 450 mg for I.V. Infusion	Nippon Boehringer Ingelheim Co., Ltd.	November 16, 2022
Fenfluramine hydrochloride Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	November 16, 2022
Selumetinib sulfate Koselugo Capsules 10 mg, 25 mg	Alexion Pharma Godo Kaisha	November 16, 2022
Rivaroxaban*3 Xarelto tablets 2.5 mg	Bayer Yakuhin Ltd.	October 24, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	October 19, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) COMIRNATY RTU intramuscular injection (Bivalent: Original/Omicron BA.4-5)	Pfizer Japan Inc.	October 7, 2022
Fesoterodine fumarate*4 Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	September 26, 2022
Aflibercept (genetical recombination) *5 Eylea solution for IVT inj. 40 mg/mL	Bayer Yakuhin Ltd.	September 26, 2022
Upadacitinib hydrate*6 [1] Rinvoq Tablets 7.5 mg, [2] 15 mg, [3] 30 mg, [4] 45 mg	AbbVie GK	September 26, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)*7 Spikevax Intramuscular Injection (Bivalent: Original/Omicron BA.1)	Moderna Japan Co., Ltd.	September 20, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)*8 Comirnaty RTU intramuscular injection (Bivalent: Original/Omicron BA.1)	Pfizer Japan Inc.	September 14, 2022
Ethyl icosapentate Epadel EM Capsules 2 g	Mochida Pharmaceuticals Co. Ltd.	September 12, 2022
Sutimlimab (genetical recombination) Enjaymo for I.V. infusion 1.1 g	Sanofi K.K.	September 8, 2022

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

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

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

*4 A drug with a new additional pediatric dosage indicated for urinary management in patients with neurogenic bladder

*5 Retinopathy of prematurity

*6 [1] [2] [3] Remission induction and maintenance therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments), [4] remission induction therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments)

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

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

(Reference)

Terminology of “Phaeochromocytoma” in the Precautions of Drugs (Excluding *in vitro* Diagnostics)

1. Introduction

In principle, "phaeochromocytoma" should be changed to "phaeochromocytoma or paraganglioma" for drug products for which attention is called for as "phaeochromocytoma" in the Precautions of electronic package inserts.

2. Background

In the Precautions of electronic package inserts, the term "phaeochromocytoma" has been used, but in the "Clinical Practice Guideline of Pheochromocytoma and Paraganglioma 2018" ("Investigation of Malignant Pheochromocytoma and Preparation of Clinical Guidelines" Committee, the Japan Endocrine Society (ed.)), "phaeochromocytoma," which has been conventionally used as a general term for phaeochromocytoma and paraganglioma, is newly defined as "phaeochromocytoma/paraganglioma." Specifically, the guideline defines phaeochromocytoma (PCC) as primary adrenal cases, paraganglioma (PGL) as extra-adrenal paraganglionic origin cases, and phaeochromocytoma/paraganglioma (PPGL) as encompassing both.

In line with the above, as a result of reviewing the terminology used for the drug products for which a precautionary statement regarding "phaeochromocytoma" has already been included in the Precautions, it was decided to change the current term "phaeochromocytoma" to "phaeochromocytoma or paraganglioma." Specific revisions of electronic package inserts will be considered individually by the MAHs, and they will be implemented after consultation with the PMDA.

3. Points to be noted in the future

In the Precautions of electronic package inserts, the term of drug products for which a precautionary statement regarding "phaeochromocytoma" has been included will be changed to "phaeochromocytoma or paraganglioma" in due course. Based on the currently issued guideline, the term "phaeochromocytoma" listed as an adverse drug reaction, etc. is likely to include paraganglioma. Healthcare professionals are requested to take note of this.