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Report on Investigation Results

October 29, 2024

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Esaxerenone, eplerenone, potassium iodide
[Brand name]	See Appendix 1.
[Marketing authorization holder]	See Appendix 1.
[Indications]	See Appendix 1.
[Dosage and administration]	See Appendix 1.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Eplerenone and esaxerenone are mineralocorticoid receptor antagonists that selectively inhibit the binding of aldosterone to mineralocorticoid receptors. Eplerenone is indicated for "hypertension" and "chronic cardiac failure," [1] and esaxerenone is indicated for "hypertension."

While potassium iodide preparations are used for the treatment of diseases such as goitre and tertiary syphilis, their indications vary among drug products. Potassium iodide preparations shown in Appendix 1 are indicated for "prevention/reduction of internal exposure of the thyroid gland to radioactive iodine (hereinafter referred to as "prevention/reduction of internal exposure")" and are used as so-called "stable iodine preparations" in nuclear disasters.

Eplerenone and esaxerenone may induce hyperkalaemia by their potassium retention effects. Both the drugs were approved only for the indication of hypertension at the time of initial approval. Since co-administration of these drugs with potassium preparations may

[1] The approved indication is as follows: "Patients with the following disease who are receiving basic treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, β-blockers, diuretics, etc.: Chronic cardiac failure"

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increase the risk of hyperkalaemia, such co-administration has been contraindicated. When chronic cardiac failure was added to the indications of eplerenone subsequently, co-administration with potassium preparations in cases for the indication of chronic cardiac failure was listed in the Precautions for Co-administration section. This decision was based on considerations of the factors including medical needs and feasibility of risk minimization (monitoring of serum potassium level and dose adjustment), because diuresis should be promoted in treatment of patients with cardiac failure accompanied by excessive fluid retention, which poses a concern about the occurrence of hypokalaemia, thereby resulting in the necessity of administering potassium preparations.

In order to ensure consistency with the descriptions in PRECAUTIONS for eplerenone and esaxerenone, PRECAUTIONS for potassium preparations was revised. In August 2024, PRECAUTIONS for potassium iodide preparations was revised to uniformly list esaxerenone and eplerenone in the Contraindications for Co-administration section (for eplerenone, only co-administration for the indication of hypertension is contraindicated).

In response to this revision, the Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as “MHLW”) issued the "Notification on Request of Investigation Related to the Safety of Drugs, etc." (PSB/PSD Notification No. 0913-3 dated September 13, 2024) requesting the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") to conduct an investigation on the possibility of lifting the contraindication for co-administration with esaxerenone or eplerenone in cases where potassium iodide preparations are used for the indication of prevention/reduction of internal exposure, with consideration given to the dosage and administration, etc. The PMDA accordingly conducted an investigation based on the request and discussed the necessity of revision of the package insert.

The PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Investigation by the PMDA

1. Potassium iodide preparations used to prevent/reduce internal exposure

1-1. Necessity of potassium iodide preparations

In the "Nuclear Regulation Authority Guide for Emergency Preparedness and Response (NRA EPR Guide)" (Nuclear Regulation Authority, established on October 31, 2012, fully revised on September 10, 2024), the development of the systems for distribution and administration of the potassium iodide preparations is listed as one of the medical systems, etc. to be developed at the time of a nuclear disaster. The following are described concerning the oral administration of stable iodine preparations:

"Radioactive iodine accumulates in the thyroid gland when taken into the body, and it increases the risk of occurrence of thyroid cancer, etc. after several years or decades, with a higher risk in younger persons. Such internal exposure of the thyroid gland to radioactive iodine can be prevented or reduced by taking stable iodine preparations at an appropriate timing. Therefore, it is necessary to be prepared for administering stable iodine preparations at an appropriate timing in cases where there is a risk of internal exposure of the thyroid gland to radioactive iodine."

1-2. Dosage and administration of potassium iodide preparations

The dosage and administration described in the package insert of potassium iodide preparations for the use of prevention/reduction of internal exposure are as follows: "The usual dose of potassium iodide for oral use is 100 mg per dose for persons aged 13 years or older, 50 mg per dose for persons aged 3 years or older and younger than 13 years old, 32.5 mg per dose for persons aged 1 month or older and younger than 3 years old, and 16.3 mg per dose for neonates." In addition, the following description is included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section: “Administration should be performed following the directions by the government, etc. for the indication of prevention/reduction of internal exposure of the thyroid gland to radioactive iodine.”

In "Distribution and Administration of Stable Iodine Preparations" (hereinafter referred to as "Manual for Administration of Stable Iodine Preparations") (Nuclear Regulation Authority, prepared on July 19, 2013, partially revised on July 21, 2021), the contents of the package insert are cited to describe the dosage of stable iodine preparations per dose, stating that

the frequency of the administration is one time in principle[2].

The dosage and administration of potassium iodide preparations for indications other than prevention/reduction of internal exposure are as follows: 0.3 to 1.0 mg per day is orally administered in 1 to 3 divided doses for goitre associated with iodine deficiency, 5 to 50 mg per day is orally administered in 1 to 3 divided doses for goitre accompanied by hyperthyroidism, and 0.1 to 0.5 g is orally administered 3 to 4 times per day for difficulty of sputum expectoration and tertiary syphilis. Potassium iodide preparations are continuously administered for a certain period of time for these indications, unlike for prevention/reduction of internal exposure, for which potassium iodide is administered for one time in principle.

1-3. Potassium content in potassium iodide preparations

The content of potassium per dose in potassium iodide preparations administered for prevention/reduction of internal exposure is 24 mg for persons aged 13 years or older, 12 mg for persons aged 3 years or older and younger than 13 years, 7.8 mg for persons aged 1 month or older and younger than 3 years, and 3.9 mg for neonates.

The content of potassium per dose in potassium preparations that are described in the Contraindications for Co-administration section in the package inserts for esaxerenone and eplerenone, as well as other information, is shown in the following table. The content of potassium per dose in potassium iodide preparations for prevention/reduction of internal exposure of 24 mg (in the case of persons aged 13 years or older) is approximately 1/65 to 1/3 of that in potassium preparations other than potassium iodide.

Table: The content of potassium per dose in potassium preparations that are described in the Contraindications for Co-administration section for esaxerenone and eplerenone

Active ingredient	Potassium chloride	Potassium gluconate	Potassium aspartate	Potassium acetate
Dosage form	a. Powders b. Elixir c. Sustained-release tablets d. Injections (for potassium correction) e. Injections (for potassium supplementation/ correction)	a. Tablets b. Fine granules	a. Tablets b. Powders c. Injections	Oral Solution

[2] This principle is based on the premise that protective measures such as evacuation of residents will be taken to avoid repeated dosing. In principle, repeated doses are to be administered only if the Nuclear Regulation Authority determines the necessity of repeated dosing and the Nuclear Disaster Countermeasures Headquarters or the local government gives a direction based on that determination.

Indications	a. b. e. Potassium supplementation, hypochloraemic alkalosis c. Improvement of hypokalaemia d. e. Electrolyte correction for electrolyte replenisher	a. b. Potassium supplementation when potassium level is low	a. b. c. Potassium supplementation	Potassium supplementation
Dosage and administration	a. b. 2 to 10 g per day is orally administered in several divided doses. c. 1,200 mg is orally administered twice daily after meals. d. Potassium chloride is added to electrolyte replenisher for intravenous drip infusion or added to peritoneal dialysate for intraperitoneal administration. e. 0.75 to 3 g is diluted with a suitable diluent and injected intravenously.	a. b. The amount equivalent to 10 mEq of potassium is orally administered 3 to 4 times daily.	a. b. 0.9 to 2.7 g per day is orally administered in 3 divided doses. c. 1.71 to 5.14 g is diluted with a suitable diluent and injected intravenously.	5.7 g per day is orally administered as a diluted solution in 3 divided doses.
Content of potassium per dose	a., c. 262 to 1,311 mg b. 629 mg d. 782 mg (maximum content per hour) e. 391 to 1,564 mg	a., b. 391 mg	a., b. 68.5 to 617 mg c. 391 to 1,174 mg	757mg

- Since the indications and dosage and administration described in the table are simplified, the electronic package insert should be referred to for the approved indications and dosage and administration.
- The usual dosage and administration for adults are described for the dosage and administration. The amount of the active ingredient is described as the dose.
- The content of potassium per dose was calculated by converting 1 mEq to 39.1 mg when mEq values are provided. If mEq values are not provided, the content was calculated using the following formula: Dose (mg) x 39.1/molecular weight. In addition, when the number of doses per day is described as "several times" or "3 to 4 times" in the DOSAGE AND ADMINISTRATION section, the content per dose was calculated assuming that the drug is administered 4 times daily.

Descriptions in "Standard Tables of Food Composition in Japan" (Subdivision on Resource Study, the Council for Science and Technology, Ministry of Education, Culture, Sports, Science and Technology, 2015) are quoted in Manual for Administration of Stable Iodine Preparations. According to the descriptions, the ratios of the content of potassium per dose in potassium iodide preparations administered for prevention/reduction of internal exposure of 24 mg (for persons aged 13 years or older) to the content in 100 g of edible portion of following foods are as follows: 1:4 for bread, 1:15 for banana, 1:29 to 1:28 for fermented soybean, 1:23 of for baked sweet potato, 1:18 to 1:16 for raw skipjack tuna, and 1:15 for grilled sardine. It is described, therefore, that the possibility that potassium in potassium

iodide preparations causes a health hazard is extremely low if an appropriate amount is administered.

2. Descriptions in overseas product labeling

The descriptions in the overseas product labeling of the investigated drugs are as follows (See appendix 2).

<Esaxerenone>

Esaxerenone is not marketed overseas.

<Eplerenone>

- In the U.S. product labeling, concomitant use with potassium supplements is contraindicated only for the treatment of hypertension.
- In the Summary of Product Characteristics in Europe, concomitant use with potassium supplements is not contraindicated. It is described that the use of potassium supplements after initiation of treatment with eplerenone is not recommended, due to a risk of hyperkalaemia.

<Potassium iodide>

- In the U.S. product labeling, there is no precautionary statement for co-administration with esaxerenone or eplerenone.
- In the Interaction with other medicinal products and other forms of interaction section in the Summary of Product Characteristics in Europe, a precaution regarding the possibility of hyperkalaemia that results from co-administration with aldosterone antagonists[3] is included.

3. Descriptions in the guidelines, etc.

In the Japanese and overseas guidelines on the use of potassium iodide in the event of a nuclear disaster, whether there is any description about the use of potassium iodide in combination with esaxerenone or eplerenone or the occurrence of hyperkalaemia resulting from the concomitant use was confirmed.

- In "Guidelines for Iodine Prophylaxis as a Protective Measure: Information for

[3] At present, aldosterone antagonist is described as mineralocorticoid receptor antagonist in the clinical practice guidelines, etc.

Physicians" (Japan Medical Association, March 2014), potassium-sparing diuretics are listed as drugs that may cause interactions in individuals receiving the treatment, and eplerenone is listed as a potassium-sparing diuretic in the list of drugs that require a caution for the interactions. However, it is described that the number of administrations of a stable iodine preparation associated with an accident at a nuclear power facility is limited to one time in principle, and there may be little concern about serious adverse health effects due to the co-administration.

- There is no relevant description in Iodine thyroid blocking: Guidelines for use in planning and responding to radiological and nuclear emergencies (WHO 2017).
- There is no relevant description in the U.S. FDA Guidance Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies (2001).
- There is no relevant description in the U.S. FDA Guidance for Industry. KI in Radiation Emergencies−Questions and Answers (2002).
- There is no relevant description in the Frequently Asked Questions on Potassium Iodide (KI) posted on the website of the U.S. FDA (the last confirmation was made on September 18, 2022).

IV. PMDA's judgment based on the investigation results

1. Concomitant use of potassium iodide with eplerenone or esaxerenone

Based on the results of "III. Investigation by the PMDA" above, from the following viewpoints, the PMDA considers it appropriate to list concomitant use of potassium iodide with esaxerenone or eplerenone in the Precautions for Co-administration section instead of uniformly limiting the use of potassium iodide in patients receiving esaxerenone or eplerenone, in cases where potassium iodide preparations are used to prevent/reduce internal exposure.

- It has been reported that if radioactive substances are released to the surrounding environment as a result of a nuclear disaster, the risk of thyroid cancer, etc. after several years or several decades increases because of the effects of internal exposure to radioactive iodine. Such internal exposure of the thyroid gland to radioactive iodine can be prevented by taking potassium iodide at an appropriate timing. (See "III. 1-1. Necessity of potassium iodide preparations.")

- When potassium iodide preparations are used for prevention/reduction of internal exposure, they should be administered only once, in principle, in contrast to cases for other indications and for other potassium preparations (preparations intended for potassium supplementation, etc.). In addition, potassium content per dose for prevention/reduction of internal exposure is as low as 24 mg, which does not exceed 1/3 of the potassium content per dose of other potassium preparations, and it is not high compared to that contained in foods. Therefore, when potassium iodide preparations are used to prevent/reduce internal exposure, the risk of hyperkalaemia associated with concomitant use with esaxerenone or eplerenone is considered to be lower than that with other potassium preparations. (See "III. 1-2. Dosage and administration of potassium iodide preparations" and "III. 1-3. Potassium content in potassium iodide preparations.")
- In the U.S. product labeling of eplerenone, concomitant use of potassium supplements is contraindicated. However, in the product labeling of potassium iodide (as a thyroid blocker in nuclear radiation emergency), eplerenone is not contraindicated for co-administration. In addition, in the Summary of Product Characteristics in Europe for eplerenone or potassium iodide (as a thyroid blocker in nuclear radiation emergency), neither potassium iodide nor eplerenone is contraindicated for co-administration, respectively. It should be noted that esaxerenone is not marketed overseas. (See "III. 2 Descriptions in overseas product labeling.")
- There is no description that the use of potassium iodide in combination with esaxerenone or eplerenone is contraindicated in the Japanese and overseas guidelines on the use of potassium iodide in the event of a nuclear disaster. (See "III. 3 Descriptions in the guidelines, etc.")

V. Expert Discussion

1. Co-administration of potassium iodide preparations with eplerenone or esaxerenone

The decision by the PMDA as follows was supported by all the expert advisors: It is appropriate to list concomitant use of potassium iodide with esaxerenone or eplerenone in the Precautions for Co-administration section instead of uniformly limiting the use of

potassium iodide in patients receiving esaxerenone or eplerenone, in cases where potassium iodide preparations are used to prevent/reduce internal exposure.

VI. Overall evaluation

The PMDA concluded that PRECAUTIONS may be revised according to Appendix 3 based on the above discussions. (Appendix 3 is not included in this document. See “Detailed information on revisions of PRECAUTIONS” on the PMDA’s website.)

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Appendix 1

List of investigated drugs

Non-proprietary name	Brand name	Marketing authorization holder	Indications	Dosage and administration
Esaxerenone	Minnebro Tablets 1.25 mg, 2.5 mg, 5 mg, Minnebro OD Tablets 1.25 mg, 2.5 mg, 5 mg	Daiichi Sankyo Co., Ltd.	Hypertension	The usual daily dose of esaxerenone for adults is 2.5 mg once daily administered orally. If blood pressure is not adequately controlled, the dose can be increased to 5 mg.
Eplerenone	Selara Tablets 25 mg, 50 mg, 100 mg, and the others	Viatris Pharmaceuticals Japan G.K. and the others	<Selara Tablets 25 mg/50 mg/100 mg> Hypertension <Selara Tablets 25 mg/50 mg> Patients with the following disease who are receiving basic treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, β-blockers, diuretics, etc.: Chronic cardiac failure	<Hypertension> The usual starting dose of eplerenone for adults is 50 mg administered once daily. If blood pressure is not adequately controlled, the dose can be increased to 100 mg. <Chronic cardiac failure> The usual starting dose of eplerenone for adults is 25 mg administered once daily. The dose should be increased to 50 mg once daily after approximately 4 weeks or more from the start of treatment, taking into account the serum potassium level and patients' condition. However, in patients with moderate renal impairment, the starting dose should be 25 mg administered once every other day and the maximum daily dose should be 25 mg per dose. According to the serum potassium levels and patients'

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Non-proprietary name	Brand name	Marketing authorization holder	Indications	Dosage and administration
				condition, the dose should be reduced or administration should be suspended as appropriate.
Potassium iodide	Potassium Iodide "Nichi-iko"	Nichi-Iko Pharmaceutical Co., Ltd.	•Goitre (that is due to iodine deficiency and that is accompanied by hyperthyroidism) •Difficulty of sputum expectoration associated with the following diseases: Chronic bronchitis, asthma •Tertiary syphilis •Prevention/reduction of internal exposure of the thyroid gland to radioactive iodine	<Goitre (that is due to iodine deficiency)> The dosage of potassium iodide for oral use is 0.3 to 1.0 mg daily in 1 to 3 divided doses. The dose should be adjusted depending on the age or symptoms of the patients. <Goitre (that is accompanied by hyperthyroidism)> The adult dosage of potassium iodide for oral use is 5 to 50 mg daily in 1 to 3 divided doses. In this case, the indication should be carefully considered. The dose should be adjusted depending on the age or symptoms of the patients. <Difficulty of sputum expectoration (that is associated with chronic bronchitis, asthma), tertiary syphilis> The usual daily dose of potassium iodide for adults is 0.1 to 0.5 g administered orally 3 or 4 times daily. The dose should be adjusted depending on the age or symptoms of the patients. <Prevention/reduction of internal exposure of the thyroid gland to radioactive iodine> The usual dose of potassium iodide for oral use is 100 mg for persons aged 13 years or older, 50 mg for persons aged 3 years or older and younger than 13 years old,
	Potassium Iodide "Hoei"	Viatris Healthcare G.K.		

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Non-proprietary name	Brand name	Marketing authorization holder	Indications	Dosage and administration
				32.5 mg for persons aged 1 month or older and younger than 3 years old, and 16.3 mg for neonates.
Potassium iodide	Potassium Iodide Pills 50 mg “Nichi-iko”	Nichi-Iko Pharmaceutical Co., Ltd.	•Goitre (that is accompanied by hyperthyroidism) •Difficulty of sputum expectoration associated with the following diseases: Chronic bronchitis, asthma •Tertiary syphilis •Prevention/reduction of internal exposure of the thyroid gland to radioactive iodine	<Goitre (that is accompanied by hyperthyroidism)> The dosage of potassium iodide for oral use is 5 to 50 mg daily in 1 to 3 divided doses. In this case, the indication should be carefully considered. The dose should be adjusted depending on the age or symptoms of the patients. <Difficulty of sputum expectoration associated with chronic bronchitis and asthma, tertiary syphilis> The usual dosage of potassium iodide for adults is 0.1 to 0.5 g administered orally 3 or 4 times daily. The dose should be adjusted depending on the age or symptoms of the patients. <Prevention/reduction of internal exposure of the thyroid gland due to radioactive iodine> The usual dose of potassium iodide for oral use is 100 mg for persons aged 13 years or older, 50 mg for persons aged 3 years or older and younger than 13 years old, 32.5 mg for persons aged 1 month or older and younger than 3 years old, and 16.3 mg for neonates.
Potassium iodide	Potassium Iodide Oral Jelly 16.3 mg “Nichi-iko”,	Nichi-Iko Pharmaceutical Co., Ltd	Prevention/reduction of internal exposure of the thyroid gland to radioactive iodine	The usual dose of potassium iodide for oral use is 100 mg for patients aged 13 years or older, 50 mg for patients aged 3 years or older and younger than 13 years old,

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Non-proprietary name	Brand name	Marketing authorization holder	Indications	Dosage and administration
	32.5 mg “Nichi-iko”			32.5 mg for patients aged 1 month or older and younger than 3 years old, and 16.3 mg for neonates.

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Appendix 2

Current descriptions of overseas product labeling

Esaxerenone

US prescribing information (USPI)	European summary of product characteristics (SmPC)
Not marketed	Not marketed

Eplerenone

US prescribing information (USPI) (July 2023 version)	European summary of product characteristics (SmPC) (December 8, 2022 version)
4 CONTRAINDICATIONS *For Patients Treated for Hypertension* INSPRA is contraindicated for the treatment of hypertension in patients with: • concomitant administration of potassium supplements or potassium-sparing diuretics (e.g., amiloride, spironolactone, or triamterene) *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), Drug Interactions (7), and Clinical Pharmacology (12.3)].*	**4.4 Special warnings and precautions for use** *Hyperkalaemia* Consistent with its mechanism of action, hyperkalaemia may occur with plerenone. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. Thereafter, periodic monitoring is recommended especially in patients at risk for the development of hyperkalaemia, such as elderly patients, patients with renal insufficiency (see section 4.2) and patients with diabetes. The

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17 PATIENT COUNSELING INFORMATION Advise patients receiving INSPRA: • Not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician *[see Warnings and Precautions (5.1)]*.	use of potassium supplements after initiation of eplerenone therapy is not recommended, due to an increased risk of hyperkalaemia. Dose reduction of eplerenone has been shown to decrease serum potassium levels. In one study, the addition of hydrochlorothiazide to eplerenone therapy has been shown to offset increases in serum potassium. **4.5 Interaction with other medicinal products and other forms of interaction** Pharmacodynamic interactions *Potassium-sparing diuretics and potassium supplements* Due to increased risk of hyperkalaemia, eplerenone should not be administered to patients receiving other potassium-sparing diuretics and potassium supplements (see section 4.3). Potassium-sparing diuretics may also potentiate the effect of anti-hypertensive agents and other diuretics.

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Potassium iodide

US prescribing information (USPI) (August 2023 version)	European summary of product characteristics (SmPC) (May 29, 2024 version)
	4.4 Special warnings and precautions for use Potassium salts should be given cautiously to patients with renal or adrenal insufficiency, acute dehydration or heatcramp. Care should be exercised if potassium salts are given concomitantly with potassium-sparing diuretics, as hyperkalaemiamay result (see section 4.5).
No related description	**4.5 Interaction with other medicinal products and other forms of interaction** Several drugs, such as captopril and enalapril can cause hyperkalaemia and this effect may be enhanced if potassiumiodide is also administered. The effect of quinidine on the heart is increased by increased plasma concentration of potassium. Hyperkalaemia results from the interaction between potassium

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	salts and potassium sparing diuretics such as amilorideor triamterene or aldosterone antagonists (see section 4.4). The effects of iodine and iodides on the thyroid may be altered by other compounds which may also have an effect onthe thyroid, including amiodarone and lithium. The hypothyroid and goitrogenic effects of lithium carbonate and iodidescan be additive if they are given concurrently.