Report on the Deliberation Results

December 4, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Minnebro Tablets 1.25 mg Minnebro Tablets 2.5 mg Minnebro Tablets 5 mg
Non-proprietary Name	Esaxerenone (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	February 26, 2018

Results of Deliberation

In its meeting held on December 3, 2018, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

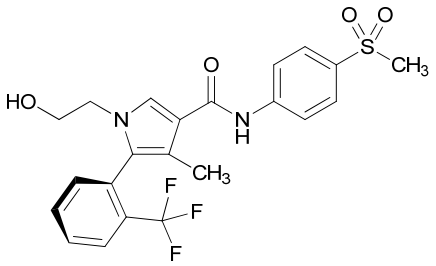
Review Report

November 12, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Minnebro Tablets 1.25 mg Minnebro Tablets 2.5 mg Minnebro Tablets 5 mg
Non-proprietary Name	Esaxerenone
Applicant	Daiichi Sankyo Company, Limited
Date of Application	February 26, 2018
Dosage Form/Strength	Each tablet contains 1.25 mg, 2.5 mg, or 5 mg of Esaxerenone.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{22}H_{21}F_3N_2O_4S$

Molecular weight: 466.47

Chemical name: (5*P*)-1-(2-Hydroxyethyl)-*N*-[4-(methanesulfonyl)phenyl]-4-methyl-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxamide

Items Warranting Special Mention None

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of hypertension, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. Hyperkalaemia associated with the product should be further evaluated.

Indication

Hypertension

Dosage and Administration

The usual adult dosage is 2.5 mg of esaxerenone administered orally once daily. The dose may be increased to 5 mg in patients whose blood pressure is not adequately controlled.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 28, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Minnebro Tablets 1.25 mg Minnebro Tablets 2.5 mg Minnebro Tablets 5 mg
Non-proprietary Name	Esaxerenone
Applicant	Daiichi Sankyo Company, Limited
Date of Application	February 26, 2018
Dosage Form/Strength	Each tablet contains 1.25 mg, 2.5 mg, or 5 mg of Esaxerenone.
Proposed Indication	Hypertension

Proposed Dosage and Administration

The usual adult dosage is 2.5 mg of esaxerenone administered orally once daily. The dose may be increased to 5 mg in patients whose blood pressure is not adequately controlled.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Esaxerenone is a nonsteroidal mineralocorticoid receptor (MR) antagonist discovered by Exelixis, Inc., (the US). It acts as a highly selective MR antagonist, but does not show detectable antagonistic action or activating effect on other steroid hormone receptors (glucocorticoid receptor [GR], progesterone receptor [PR], and androgen receptor [AR]). The MR is present in various organs, and binding of esaxerenone to MR in renal tubules causes suppression of sodium (Na) reabsorption, leading to a decrease in blood pressure.

In Japan, the applicant initiated clinical development of esaxerenone in 2010 and recently submitted a marketing application based on the results of the clinical studies in Japan, with the proposed indication of "hypertension." As of September 2018, esaxerenone is not approved in any country or region.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. The general properties of the drug substance, including description, crystallinity, solubility, hygroscopicity, melting point, dissociation constant, distribution coefficient, and crystalline polymorphism were determined. The drug substance has an enantiomer.

The chemical structure of the drug substance has been elucidated by elemental analysis, infrared spectroscopy (IR), nuclear magnetic resonance (NMR) of hydrogen-1 and carbon-13 (^{1}H-NMR, ^{13}C-NMR) spectroscopy, mass spectroscopy (MS), and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized by [redacted] processes using [redacted] and [redacted] as the starting materials. [redacted] were identified as the critical quality attributes (CQAs) (Table 1).

[redacted] is defined as the critical step. [redacted] is controlled as the critical intermediate.

Table 1. Outline of the quality control strategy for the drug substance

CQA	Controlling method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description (appearance), identification (IR), purity (related substances [high performance liquid chromatography (HPLC)], enantiomers [HPLC], residual solvents [gas chromatography (GC)]), residue on ignition, particle size (laser diffraction), and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows the main stability studies conducted on the drug substance. The photostability test showed that the drug substance is photostable.

Table 2. Main stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot-scale batches	25°C	60% RH	[redacted] low-density PE bag + high-density PE drum[a]	24 months
Accelerated testing		40°C	75% RH		6 months

a: High-density polyethylene (PE) drum stoppered with a high-density PE cap

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored at room temperature in a [redacted] low-density polyethylene (PE) bag placed in a high-density PE drum, according to "Guideline on the Evaluation for Stability Data" (ICH Q1E Guideline). Long-term testing will be continued up to 60 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a tablet containing 1.25, 2.5, or 5 mg of the drug substance. The excipients used in the drug product include lactose hydrate, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate, and yellow ferric oxide (1.25- and 2.5-mg tablets) or red ferric oxide (5-mg tablets).

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of granulation, blending, tableting, and packaging, and [redacted] has been identified as the critical step. In-process control parameters and action limits have been established for [redacted].

The strategy for quality control was developed by the following investigations, etc., using a quality-by-design (QbD) approach (Table 3).

- Identification of CQA
- Identification of critical process parameters (CPPs) based on the quality risk assessment

Table 3. Outline of the quality control strategy for the drug product

CQA	Controlling method
[redacted]	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description (appearance), identification (HPLC and ultraviolet-visible spectrum [UV/VIS]), purity (enantiomers [HPLC]), uniformity of dosage units (content uniformity testing [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows the main stability studies conducted on the drug product. A photostability test showed that the drug product was photostable.

Table 4. Main stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot-scale batches	25°C	60% RH	PTP[a] or PE bottle[b]	18 months
Accelerated testing		40°C	75% RH		6 months

a: Polypropylene (PP) + aluminum
b: PE bottle stoppered with a PP cap

Based on the above, a shelf life of 30 months has been proposed for the drug product when stored in a press through packaging (PTP) of polypropylene (PP) and aluminum foil (1.25, 2.5, and 5 mg tablets) or filled in a PE bottle stoppered with a PP cap (2.5 mg tablets) and stored at room temperature, according to ICH Q1E Guideline. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is appropriately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Effect on the binding of aldosterone to rat MR (CTD 4.2.1.1-1)

MR fraction prepared from the homogenate of isolated rat kidney was let stand for 18 hours with D-[1,2,6,7-^{3}H(N)]-aldosterone (^{3}H-aldosterone) in the presence of esaxerenone (1×10^{-10}-1×10^{-6} mol/L), spironolactone (3×10^{-10}-3×10^{-6} mol/L), eplerenone (1×10^{-8}-1×10^{-4} mol/L), or aldosterone (3×10^{-11}-3×10^{-7} mol/L), and the inhibitory effect of each drug against the binding of ^{3}H-aldosterone to rat MR was investigated. The half maximal inhibitory concentration (IC_{50}) of esaxerenone, spironolactone, eplerenone, and aldosterone was 9.43×10^{-9}, 3.57×10^{-8}, 7.13×10^{-7}, and 4.08×10^{-9} mol/L, respectively.

3.1.1.2 Binding to rat MR (CTD 4.2.1.1-2)

MR fraction prepared from the homogenate of isolated rat kidney was let stand for 18 hours with ^{3}H-aldosterone in the presence or absence of esaxerenone (3×10^{-10}-3×10^{-9} mol/L), spironolactone (3×10^{-9}-3×10^{-8} mol/L), or eplerenone (1×10^{-7}-1×10^{-6} mol/L), and Scatchard analysis was performed on the amount of ^{3}H-aldosterone bound to the receptor. All of esaxerenone, spironolactone, and eplerenone showed a competitive antagonistic effect.

3.1.1.3 Effect on the binding to rat AR, rat GR, and rabbit PR (CTD 4.2.1.1-3)

AR fraction prepared from the homogenate of isolated rat prostate, GR fraction prepared from the homogenate of isolated rat liver, and PR fraction prepared from the homogenate of rabbit uterus were let stand for 18 hours with a radiolabeled ligand for each receptor in the presence of esaxerenone (1×10^{-9}-1×10^{-5} mol/L), spironolactone (1×10^{-9}-1×10^{-5} mol/L), or eplerenone (1×10^{-8}-1×10^{-4} mol/L), and the inhibitory effect of each drug against the binding of the radiolabeled ligand to each receptor was investigated. As the positive controls, the effect of testosterone (ligand for AR, 1×10^{-10}-1×10^{-6} mol/L), dexamethasone (ligand for GR, 1×10^{-10}-1×10^{-6} mol/L), and progesterone (ligand for PR, 1×10^{-10}-1×10^{-6} mol/L) was evaluated in a similar manner. Table 5 shows the results.

Table 5. IC_{50} of each drug against AR, GR, and PR (mol/L)

	AR	GR	PR
Esaxerenone	$>1.0 \times 10^{-5}$	$>1.0 \times 10^{-5}$	$>1.0 \times 10^{-5}$
Spironolactone	1.33×10^{-7}	7.64×10^{-7}	1.20×10^{-6}
Eplerenone	$>1.0 \times 10^{-4}$	3.06×10^{-6}	$>1.0 \times 10^{-4}$
Testosterone	2.90×10^{-9}	—	—
Dexamethasone	—	2.09×10^{-9}	—
Progesterone	—	—	1.79×10^{-8}

3.1.1.4 Effect on transcriptional activity of MR (CTD 4.2.1.1-4)

Esaxerenone (2.56 pmol/L-5 μmol/L), spironolactone (2.56 pmol/L-5 μmol/L), or eplerenone (51.2 pmol/L-100 μmol/L) was added to 293A cells forced to express human or rat MR and luciferase reporter vector in the presence or absence of aldosterone, and luciferase activity was measured. By assuming the activity to be 0% in the absence of the investigational drug and aldosterone, and 100% in the absence of the investigational drug and the presence of aldosterone, IC_{50} of esaxerenone, spironolactone, and eplerenone was 3.7, 66, and 970 nmol/L, respectively, with human MR, and 4.9, 23, and 300 nmol/L, respectively, with rat MR.

3.1.1.5 Effect on transcriptional activities of steroid hormone receptors (CTD 4.2.1.1-4)

Esaxerenone (2.56 pmol/L-5 μmol/L), spironolactone (2.56 pmol/L-5 μmol/L), or eplerenone (51.2 pmol/L-100 μmol/L) was added to 293A cells forced to express human GR, PR, or AR and luciferase reporter vector in the presence or absence of the ligand for each receptor, and luciferase activity was measured. By assuming the activity to be 0% in the absence of the investigational drug and each ligand, and 100% in the absence of the investigational drug and the presence of each ligand, IC_{50} of each drug was calculated. Esaxerenone had no inhibitory or activating effect on any of the receptors. Spironolactone and eplerenone inhibited GR, PR, and AR in a concentration-dependent manner. Also, spironolactone activated PR and AR in a concentration-dependent manner. Eplerenone did not activate either of the receptors.

3.1.1.6 Pharmacological activity of metabolite R-413942 (CTD 4.2.1.1-5)

R-413942 (1.6-1000 nmol/L) or esaxerenone (1.6-1000 nmol/L) was added to 293A cells forced to express human MR, GR, PR, or AR and luciferase reporter vector in the presence or absence of the ligand for each receptor, and luciferase activity was measured. Similar to esaxerenone, R-413942 inhibited the activity of human MR in a concentration-dependent manner, but the inhibitory activity was approximately 1/25 times that of esaxerenone, and R-413942 did not activate human MR up to 1000 nmol/L. R-413942 did not inhibit or activate human GR, PR, or AR.

3.1.2 *In vivo* studies

3.1.2.1 Effect on aldosterone-induced decrease in Na^+/K^+ concentration ratio in urine of bilaterally adrenalectomized rats (CTD 4.2.1.1-6)

Bilaterally adrenalectomized male Sprague-Dawley (SD) rats (5-week-old, n = 8/group) received orally a single dose of esaxerenone (0.3, 1.0, or 3.0 mg/kg), spironolactone or eplerenone (each 3.0, 10, or 30 mg/kg), or vehicle, followed by subcutaneous administration of aldosterone (2 μg/kg) or vehicle after 1 hour. At 1 hour after administration of aldosterone, physiological saline was administered intraperitoneally and, at 4 hours after administration of aldosterone, urine samples were collected and measured for sodium ion (Na^+) and potassium ion (K^+) concentrations. Table 6 shows the Na^+/K^+ ratio in urine.

Table 6. Effect of single oral administration of esaxerenone, spironolactone, or eplerenone on aldosterone-induced decrease in urinary Na^+/K^+ ratio in urine of bilaterally adrenalectomized rats

	Dose (mg/kg)	Urinary Na^+/K^+ ratio
Control (without aldosterone)	0	4.65
Vehicle	0	0.59
Esaxerenone	0.30	2.94
	1.0	2.37
	3.0	3.93
Spironolactone	3.0	2.66
	10	4.93
	30	6.19
Eplerenone	3.0	1.77
	10	4.09
	30	4.54

3.1.2.2 Suppression of blood pressure increase in Dahl salt-sensitive hypertensive rats (CTD 4.2.1.1-7, 4.2.1.1-8, and 4.2.1.1-9)

Male Dahl salt-sensitive hypertensive rats (7-week-old, n = 10/group) were loaded with salt and, at the same time, received orally esaxerenone (0.25, 0.5, 1, or 2 mg/kg), spironolactone (10, 30, or 100 mg/kg), eplerenone (10, 30, or 100 mg/kg), or vehicle once daily for 7 weeks, and blood pressure was measured. Esaxerenone, spironolactone, and eplerenone suppressed blood pressure increase caused by salt loading. The blood pressure was significantly lower in the esaxerenone ≥0.5 mg/kg groups, the spironolactone 100 mg/kg group, and the eplerenone 100 mg/kg group, than the control group.

3.1.2.3 Effect on urinary electrolytes in cynomolgus monkeys (CTD 4.2.1.1-10)

Esaxerenone (0.1, 0.3, or 1 mg/kg), eplerenone (10 or 30 mg/kg), or vehicle was administered orally as a single dose to male cynomolgus monkeys (3-years-old, n = 10/group). Urine was collected during 2 periods, from 0 to 8 hours after administration and from 8 to 24 hours after administration, and subjected to measurement of urine volume and Na^+ and K^+ concentrations in urine. Esaxerenone at ≥0.3 mg/kg and eplerenone at ≥10 mg/kg increased the Na^+/K^+ ratio in the urine collected from 0 to 8 hours after administration. Urine volume did not change regardless of the dose, or the period of urine collection in either group.

3.2 Secondary pharmacodynamics

3.2.1 Inhibition of receptors, channels, transporters, and enzymes (CTD 4.2.1.2-1)

The inhibitory effect of esaxerenone (10 μmol/L) against receptors, channels, transporters, and enzymes (68 types in total) was evaluated by *in vitro* radioligand binding assays and enzyme assays. Esaxerenone inhibited none of them by ≥50%.

3.3 Safety pharmacology

Table 7 shows the results of safety pharmacology studies.

Table 7. Summary of safety pharmacology studies

Organ system	Test system	Evaluation item, method, etc.	Dose	Route of administration	Findings	CTD
Central nervous system	F344 rats (6 males/group)	Irwin method	0, 10, 100, 1000 mg/kg	p.o.	No effect	4.2.1.3-4
Cardiovascular system	CHO cells introduced with hERG	hERG current	0, 3, 10, 30 μmol/L	*In vitro*	22.5% and 52.2% suppression of hERG current in 10 and 30 μmol/L groups, respectively, compared with the control group	4.2.1.3-1
	Guinea pig papillary muscle	Action potential measured by microelectrode method	0, 0.74, 2.24 μmol /L	*In vitro*	No effect	4.2.1.3-2
	Cynomolgus monkeys (4 males/group)	Blood pressure, heart rate, electrocardiogram	0, 10, 100, 1000 mg/kg	p.o.	No effect	4.2.1.3-3
Respiratory system	F344/DuCrlCrlj rats (8 males/group)	Respiratory rate, tidal volume, minute ventilation volume	0, 10, 100, 1000 mg/kg	p.o.	No effect	4.2.1.3-5

3.R Outline of the review conducted by PMDA

3.R.1 Effect on hypertension

PMDA's view:

Results of *in vitro* and *in vivo* studies on esaxerenone demonstrated that esaxerenone inhibited MR within the range of concentrations and doses tested and decreased blood pressure of Dahl salt-sensitive hypertensive rats in a dose-dependent manner. These results suggest that esaxerenone would also be effective in lowering blood pressure in humans. The results of *in vitro* studies suggest that esaxerenone is more highly selective to MR than drugs in the same class, but how the selectivity of esaxerenone affects the clinical efficacy and safety should also be evaluated based on the results of clinical studies [see Section "7.R. Outline of the review conducted by PMDA"].

3.R.2 Safety pharmacology studies

The applicant's explanation about the effect of esaxerenone on the cardiovascular system:

In Chinese hamster ovary (CHO) cells introduced with human ether-á-go-go related gene (hERG), esaxerenone at 10 and 30 mmol/L suppressed hERG current by 22.5% and 52.2%, respectively, compared with the control group. However, esaxerenone is unlikely to have any clinically significant

effect on the cardiovascular system for the following reasons: (1) C_{max} of esaxerenone following the administration of esaxerenone at the maximum daily clinical dose of 5 mg was 1.73 ng/mL (steady state level of esaxerenone in protein-unbound form estimated from the dose exploration study in patients with type 2 diabetes mellitus with albumin urea [Study J202]), which was 1/7496 times the concentration of esaxerenone that suppressed hERG current (10 μmol/L [12,968 ng/mL]) in CHO cells introduced with hERG, (2) esaxerenone up to 2.24 mol/L, the maximum concentration tested, had no effect on the myocardial action potential of isolated guinea pig papillary muscle preparation, and (3) single oral dose of esaxerenone up to 1000 mg/kg had no effect on the cardiovascular system of cynomolgus monkeys in a single dose titration study.

PMDA concluded that esaxerenone had no cardiovascular effect of any particular clinical concern, taking account of the explanation of the applicant. PMDA also concluded that other safety pharmacology studies did not show results of any concern about the clinical use of esaxerenone.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Plasma concentrations of esaxerenone and R-413942 (*N*-dehydroxyethyl esaxerenone), the main metabolite of esaxerenone, were measured by liquid chromatography and tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation of esaxerenone and R-413942 in plasma was 0.100 ng/mL in both rats and cynomolgus monkeys. Radioactivity after administration of ^{14}C-esaxerenone was determined by a liquid scintillation counter (LSC). ^{14}C-esaxerenone and its metabolites in plasma and excreta were measured by radio-HPLC and LC-MS/MS.

Unless otherwise specified, pharmacokinetics (PK) parameters are expressed as the mean or mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 and 4.2.2.2-2)

Table 8 shows PK parameters of esaxerenone following a single oral or intravenous administration of esaxerenone to male rats and male cynomolgus monkeys.

Table 8. PK parameters of esaxerenone following a single-dose administration of esaxerenone

Animal species	Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)	F (%)	CL[b] (mL/min/kg)	V_{ss} (L/kg)
Rats	p.o.	0.1	15.5 ± 5.0	4.0	195 ± 57	6.05 ± 1.39	61.0 ± 18.0	9.29 ± 3.33	—
		0.3	72.3 ± 31.2	3.0	1050 ± 520	6.90 ± 0.92	109 ± 54	5.72 ± 2.64	—
		1	267 ± 89	4.0	3690 ± 830	6.63 ± 0.49	127 ± 29	4.67 ± 0.87	—
		3	1080 ± 220	1.5	14,700 ± 5200	6.54 ± 0.85	102 ± 36	3.70 ± 1.09	—
	i.v.	0.1	—	—	319 ± 64	5.89 ± 1.06	—	5.38 ± 0.96	2.08 ± 0.35
		0.3	—	—	963 ± 378	7.07 ± 1.10	—	6.08 ± 3.10	2.49 ± 1.06
		1	—	—	2900 ± 1350	6.15 ± 0.36	—	6.69 ± 2.82	2.44 ± 0.85
		3	—	—	14,400 ± 1900	6.63 ± 0.29	—	3.53 ± 0.47	1.47 ± 0.28
Cynomolgus monkeys	p.o.	0.1	26.7 ± 2.3	4.0	364 ± 101	9.57 ± 2.44	69.6 ± 16.4	4.85 ± 1.30	—
		0.3	107 ± 2	3.0	1290 ± 110	10.0 ± 0.8	73.8 ± 6.5	3.90 ± 0.34	—
		1	233 ± 56	2.0	3000 ± 1140	13.0 ± 3.1	63.7 ± 13.3	6.04 ± 1.68	—
		3	1080 ± 130	3.0	13,400 ± 2600	12.3 ± 1.9	72.3 ± 6.6	3.85 ± 0.73	—
	i.v.	0.1	—	—	519 ± 24	11.6 ± 1.3	—	3.22 ± 0.15	1.34 ± 0.11
		0.3	—	—	1760 ± 270	11.5 ± 0.5	—	2.88 ± 0.46	1.36 ± 0.23
		1	—	—	4600 ± 720	11.1 ± 1.3	—	3.69 ± 0.52	1.54 ± 0.14
		3	—	—	18,600 ± 3800	13.1 ± 3.3	—	2.79 ± 0.67	1.36 ± 0.27

n = 4/group
a: Median
b: CL/F in oral administration

4.1.2 Repeated-dose studies

4.1.2.1 Six-month repeated-dose study in rats (CTD 4.2.3.2-3)

Table 9 shows PK parameters of esaxerenone in 6-month repeated oral administration of esaxerenone to male and female rats.

Table 9. PK parameters of esaxerenone in repeated oral administration of esaxerenone

Dose (mg/kg/day)	Measuring timepoint (Day)	C_{max} (ng/mL)		$AUC_{0\text{-}24}$ (ng·h/mL)	
		Male	Female	Male	Female
3	1	385 ± 43	385 ± 79	4950 ± 480	5550 ± 1260
	182	521 ± 44	718 ± 121	6810 ± 590	9950 ± 1400
30	1	2300 ± 270	2350 ± 470	34,400 ± 4800	36,900 ± 6700
	182	1740 ± 150	3080 ± 230	24,900 ± 2400	47,400 ± 600
100	1	4880 ± 870	5030 ± 720	78,500 ± 10,300	93,300 ± 12,100
	182	3410 ± 270	5840 ± 670	60,300 ± 8600	98,600 ± 21,400

n = 4/sex/group

4.1.2.2 Nine-month repeated-dose study in cynomolgus monkeys (CTD 4.2.3.2-6)

Table 10 shows PK parameters of esaxerenone in 9-month repeated oral administration of esaxerenone to male and female cynomolgus monkeys.

Table 10. PK parameters of esaxerenone in repeated oral administration of esaxerenone

Dose (mg/kg/day)	Measuring timepoint (Day)	C_{max} (ng/mL)		AUC_{∞} (ng·h/mL)	
		Male	Female	Male	Female
10	1	266 ± 37	310 ± 72	4200 ± 350	4450 ± 1180
	91	418 ± 60	576 ± 183	7440 ± 1730	8330 ± 3620
	273	437 ± 88	440 ± 103	7210 ± 1210	7150 ± 1040
100	1	619 ± 237	995 ± 261	10,600 ± 3900	12,000 ± 3300
	91	1090 ± 530[a]	1520 ± 500	18,700 ± 9500[a]	20,300 ± 6300
	273	1280 ± 870[a]	1730 ± 660	21,300 ± 17,600[a]	27,100 ± 11,600
300	1	1390 ± 720	1800 ± 1490	19,500 ± 12,600	23,200 ± 22,100
	91	1600 ± 230	2520 ± 1380	23,900 ± 4800	37,500 ± 22,700
	273	2520 ± 1210	2210 ± 1060	38,100 ± 22,900	31,000 ± 18,500

n = 4/sex/group
a: Data obtained from 3 animals

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3-1 and 4.2.2.3-2)

A single dose of ^{14}C-esaxerenone (1 mg/kg) was administered orally to male albino rats, and tissue distribution of radioactivity was evaluated by quantitative whole-body autoradiography at 2, 8, 24, 48, 72, and 168 hours after administration (n = 1/timepoint). In all tissues evaluated, the radioactivity concentration reached the maximum level at 2 or 8 hours after administration. The maximum radioactivity concentration was particularly high compared with that in blood (154 ng eq./g) in the following tissues: Large intestine (4520 ng eq./g), liver (3920 ng eq./g), Harderian gland (2750 ng eq./g), and adrenal gland (2020 ng eq./g). Radioactivity concentrations in the cerebrum and in the cerebellum were lower than that in blood at all measuring timepoints. At 48 hours after administration, radioactivity concentration was below the lower limit of quantitation in most of the tissues examined, whereas radioactivity was detected in the Harderian gland, liver, and large intestinal content 168 hours after administration.

A single dose of ^{14}C-esaxerenone (1 mg/kg) was administered orally to male pigmented rats, and tissue radioactivity concentration was measured at 2, 8, 24, 48, 72, 168, and 366 hours after administration (n = 3/timepoint). The radioactivity concentration reached the maximum level at 2 hours after administration in most of the tissues. Radioactivity was detected in blood, eyeballs, the liver, kidney, and spleen 336 hours after administration.

4.2.2 Placental transfer (CTD 4.2.2.3-3)

A single dose of ^{14}C-esaxerenone (1 mg/kg) was administered orally to rats on gestation day 18 and, tissue distribution of radioactivity in maternal animals and fetuses was evaluated by quantitative whole-body autoradiography at 2, 6, 24, and 48 hours after administration (n = 1/timepoint). In the maternal animals, radioactivity concentration in each tissue reached the maximum level at 2 or 6 hours after administration, and radioactivity concentrations in ovary, placenta, and uterus were higher than that in blood at any measuring timepoints. The maximum radioactivity concentration in ovary, placenta, and uterus was 746, 537, and 711 ng eq./g, respectively, and the maximum radioactivity concentration in blood of maternal animals was 264 ng eq./g. The radioactivity concentrations in fetuses reached the maximum level of 329 ng eq./g in liver, 189 ng eq./g in lung, 163 ng eq./g in kidney, and 149 ng eq./g in brain at 6 hours after administration. The radioactivity concentration in fetal liver and kidney was higher than that in the blood of maternal animals at 6 and 24 hours after administration, respectively, but decreased to approximately 1/10 times the maximum concentration at 48 hours after administration.

4.2.3 Protein binding (CTD 4.2.2.3-4)

Following the addition of esaxerenone at 0.06 to 6.43 μmol/L (final concentration) to plasma of rats and cynomolgus monkeys, the protein binding was 98.2% to 98.4% in rats and 96.9% to 97.7% in cynomolgus monkeys, showing a constant protein binding regardless of esaxerenone concentration in both animal species.

4.2.4 Distribution in blood cells (CTD 4.2.2.3-5)

Following the addition of ^{14}C-esaxerenone at 0.06 to 6.43 μmol/L (final concentration) to blood of rats, dogs, and cynomolgus monkeys, the distribution in blood cells was 27.3% to 29.9% in rats, 29.6% to 30.6% in dogs, and 37.8% to 39.9% in cynomolgus monkeys. The distribution in blood cells was constant regardless of esaxerenone concentration in all animal species tested.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4-11)

Liver microsomes of rats and monkeys were incubated with ^{14}C-esaxerenone (final concentration 5 μmol/L) at 37°C for 2 hours in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) or uridine 5'-diphosphoglucuronic acid (UDPGA). In both animal species, A200-7709 (esaxerenone with carboxylated N-alkyl side chain), A200-5386 (hydroxymethylated esaxerenone), and R-413942 were detected in the presence of NADPH, and A200-4164 (*O*-glucuronide of esaxerenone) was detected in the presence of UDPGA.

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma (CTD 4.2.2.4-6 and 4.2.2.4-7)

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to male rats (n = 3), the unchanged esaxerenone was the predominant form observed in plasma at 2 and 6 hours after administration (corresponding to 76.6% ± 4.2% and 78.3% ± 6.4%, respectively, of the total radioactivity concentration in plasma at 2 and 6 hours after administration). The main metabolite observed in plasma was M10 (dioxygen adduct of A200-7709; 10.9% ± 1.8% and 12.3% ± 2.9%).

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to male cynomolgus monkeys (n = 3), the unchanged esaxerenone was the predominant form observed in plasma at 2 and 6 hours after administration (49.0% ± 23.0% and 77.8% ± 9.6%, respectively). The main metabolite observed in plasma was A200-4164 (45.8% ± 21.9% and 15.3% ± 8.8%, respectively).

4.3.2.2. Metabolites in urine, feces, and bile (CTD 4.2.2.4-6 to 4.2.2.4-8 and 4.2.2.4-10)

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to male rats (n = 4), urinary excretion of the unchanged esaxerenone up to 24 hours after administration was minimal (percentage relative to the administered radioactivity, 0.1% ± 0.1%). Metabolites detected were A200-7709, A200-4164, and A200-5386/A200-7449, but the urinary excretion rate was ≤0.6% for each of them. The fecal excretion rate of the unchanged esaxerenone up to 48 hours after administration was 29.4% ± 4.7%, and the main metabolites detected in feces were A200-7709 (44.1% ± 3.1%) and A200-5386/A200-7449

(6.9% ± 1.7%; sum of A200-5386 and A200-7449 was calculated because they could not be measured separately).

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to male cynomolgus monkeys (n = 3), urinary excretion of the unchanged esaxerenone up to 24 hours after administration was minimal (0.7% ± 0.8%), and the main metabolite detected was A200-4164 (4.5% ± 1.7%). Up to 72 hours after administration, 42.2% ± 10.6% of the unchanged esaxerenone was excreted in feces, and the main metabolites excreted were A200-7709 (17.5% ± 0.7%) and A200-5386/A200-7449 (7.0% ± 1.0%).

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to bile duct-cannulated male cynomolgus monkeys (n = 3), mainly A200-4164 (38.3% ± 3.3%) and A200-7709 (3.6% ± 0.9%) were excreted in bile up to 48 hours after administration, and A200-4164 (5.3% ± 3.4%) was excreted in urine during the same period. No unchanged esaxerenone was detected either in bile or urine, whereas mainly the unchanged esaxerenone was excreted in feces up to 48 hours after administration (24.0% ± 4.1%).

Following a single intravenous administration of ^{14}C-esaxerenone (1 mg/kg) to bile duct-cannulated male cynomolgus monkeys (n = 3), mainly A200-4164 was excreted in bile and urine up to 48 hours after administration (41.0% ± 2.4% and 25.7% ± 2.4%, respectively). Excretion of the unchanged esaxerenone in bile was minimal (0.5% ± 0.4%) and not detected in urine. The fecal excretion rate of the unchanged esaxerenone up to 48 hours after administration was 1.7% ± 0.6%, and metabolites A200-4164, A200-7709, and A200-5386/A200-7449 were detected in feces, but the excretion rate was ≤0.1% for all of them.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (CTD 4.2.2.5-1 to 4.2.2.5-3, and 4.2.2.5-5)

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to male rats (n = 4) and male cynomolgus monkeys (n = 3), the administered radioactivity was excreted mainly in feces within 168 hours after administration (the percentage of the administered radioactivity; 91.4% ± 4.7% in rats, 82.3% ± 6.3% in cynomolgus monkeys) and minimally in urine (3.9% ± 2.4% in rats, 11.5% ± 3.7% in cynomolgus monkeys).

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to bile duct-cannulated male rats (n = 3), the administered radioactivity excreted in bile within 24 and 48 hours after administration was 41.9% ± 12.9% and 49.8% ± 14.0%, respectively.

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to bile duct-cannulated male cynomolgus monkeys (n = 3), the administered radioactivity excreted in bile, urine, and feces within 48 hours after administration were 53.1% ± 2.4%, 9.0% ± 4.4%, and 30.6% ± 4.2%, respectively. Following a single intravenous administration of ^{14}C-esaxerenone (1 mg/kg) to bile duct-cannulated male cynomolgus monkeys (n = 3), the administered radioactivity excreted in bile, urine, and feces within 48 hours after administration were 56.0% ± 2.7%, 33.0% ± 3.4%, and 4.0% ± 1.4%, respectively.

4.4.2 Excretion in milk (CTD 4.2.2.5-4)

Following a single oral administration of ^{14}C-esaxerenone (1 mg/kg) to rats during lactation period, the concentration of radioactivity in milk reached the maximum level (555 ng eq./mL) at 6.7 hours after administration and decreased to approximately 12% of the maximum level at 48 hours after administration. The concentration of radioactivity in plasma reached the maximum level (126 ng eq./mL) at 5.3 hours after administration and decreased to approximately 5% of the maximum level at 48 hours after administration. $t_{1/2}$ of radioactivity concentration in milk and plasma was 14 and 9.1 hours, respectively. AUC_{∞} of radioactivity in milk was 5.12-fold higher than that in plasma.

4.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews, PMDA concluded that the applicant's evaluation of the nonclinical pharmacokinetics is acceptable.

4.R.1 Tissue distribution

Given that the tissue distribution studies of esaxerenone in rats showed accumulation and/or slow elimination of radioactivity in tissues, PMDA asked the applicant to explain the possibility of safety concerns in humans based on the results of the nonclinical and clinical studies.

The applicant's explanation:

The tissue distribution study in albino rats showed that radioactivity disappeared more gradually and accumulated at a higher concentration in the liver and Harderian gland than in other tissues. Since Harderian gland is absent in humans, accumulation of esaxerenone or its metabolites does not pose any safety concern in clinical use of esaxerenone. The tissue distribution study in pigmented rats showed delayed disappearance of radioactivity from eyeballs as well, showing that esaxerenone or its metabolites have affinity to melanin. Therefore, the safety of esaxerenone was investigated in the liver and melanin-containing tissues (eyes and skin).

Safety in the liver was investigated by a 24-month repeated-dose carcinogenicity study in mice and by a 9-month repeated-dose toxicity study in cynomolgus monkeys. Fatty changes in hepatocytes, etc. were observed as histopathological changes in the liver, but their frequency and severity were not correlated with dose, suggesting that these findings are of limited toxicological significance. As for the safety in melanin-containing tissues, the phototoxicity study in pigmented rats did not show findings suggestive of phototoxicity of esaxerenone. Therefore, esaxerenone is unlikely to elicit phototoxicity in melanin-containing tissues. In the 6-month repeated oral dose toxicity study in rats and in the 9-month repeated oral dose toxicity study in cynomolgus monkeys, esaxerenone did not cause toxicological changes in the eye or skin up to the maximum dose used in each study (100 and 300 mg/kg/day, respectively).

Table 11 shows the incidence of adverse events related to hepatic function, those related to eye, and those related to skin observed in patients with essential hypertension in the pooled analysis of the Japanese phase II study (Study J203) and the Japanese phase III study (Study J301), and in the long-term treatment study (Study J302). In the pooled analysis of Studies J203 and J301, the incidence of adverse events related to hepatic function did not show any marked difference between treatment groups, and all events were mild in severity. Hepatic function-related adverse events in Study J302 were also

mild in severity. In the pooled analysis of Studies J203 and J301, the incidence of eye- or skin-related adverse events did not show any clear difference between the esaxerenone group and placebo group. The causality of eye- or skin-related adverse events to the study drug was assessed as unrelated except for one event each of dermatitis (esaxerenone 5 mg group) and rash generalised (esaxerenone 2.5 mg group). These adverse events were mild in severity except for one event of moderate xeroderma (esaxerenone 5 mg group). In Study J302, the incidence of eye- or skin-related adverse events was 2.7% (10 of 368 patients) and 6.5% (24 of 368 patients), respectively, but the causality to esaxerenone was assessed as unrelated in all of them. These adverse events were mild in severity except for one event of moderate chalazion. In addition, ocular tonometry and funduscopy were conducted in the Japanese phase I study (Study J102) and did not show any abnormality associated with esaxerenone.

The above results suggest that esaxerenone and its metabolites are unlikely to pose safety problems due to accumulation in the liver or melanin-containing tissues (eye and skin).

Table 11. Incidence of adverse events in Studies J203, J301, and J302 (safety analysis population)

	Pooled analysis of Studies J203 and J301				Study J302
	Placebo (n = 87)	Esaxerenone 1.25 mg (n = 83)	Esaxerenone 2.5 mg (n = 415)	Esaxerenone 5 mg (n = 426)	Esaxerenone 2.5-5 mg (n = 368)
Adverse events related to hepatic function[a]	3.4 (3)	3.6 (3)	1.7 (7)	1.9 (8)	4.9 (18)
Adverse events related to eye[b]	1.1 (1)	0 (0)	0.7 (3)	0.5 (2)	2.7 (10)
Adverse events related to skin[c]	2.3 (2)	0 (0)	1.4 (6)	3.1 (13)	6.5 (24)

% (number of subjects)

a: Events corresponding to Standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) code 20000006 to 15, or 20000208 to 9

b: Events classified into System organ class (SOC) “Eye disorders” in MedDRA (MedDRA/J)

c: Events classified into SOC “Skin and subcutaneous tissue disorders” in MedDRA (MedDRA/J)

Taking account of the data of the submitted nonclinical and clinical studies, PMDA concluded that the applicant’s explanation that clinical use of esaxerenone is unlikely to cause safety problems in the liver and melanin-containing tissues (eye and skin), the tissues where esaxerenone or its metabolites have been shown to accumulate, is appropriate.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of the following toxicology studies of esaxerenone: Repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (phototoxicity study, hemolysis study, and toxicity study of impurities).

5.1 Single-dose toxicity

No single-dose toxicity study was conducted on esaxerenone. Instead, acute toxicity of esaxerenone was evaluated based on the results of the initial dose in the 28-day repeated oral dose toxicity studies in rats and monkeys [see Section “5.2 Repeated-dose toxicity”] (Table 12).

Table 12. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	CTD
Male and female rats (F344)	p.o.	0,[a] 3, 10, 100, 1000	No acute toxicity observed in a 28-day repeated-dose oral toxicity study	>1000	4.2.3.2-1
Male and female cynomolgus monkeys	p.o.	0,[a] 10, 30, 100, 1000	No acute toxicity observed in a 28-day repeated-dose oral toxicity study	>1000	4.2.3.2-4

a: 0.5% methylcellulose solution

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in rats (28 days, 3 months, and 6 months) and in monkeys (28 days, 3 months, and 9 months) (Table 13). Decreased food consumption, reduced body weight gain, and decreased body weight were observed as changes associated with esaxerenone. In the repeated oral dose toxicity studies in rats (6 months) and monkeys (9 months), the exposure to esaxerenone ($AUC_{0\text{-}24}$) at the no observed adverse effect level (NOAEL) (3 mg/kg/day in rats, 10 mg/kg/day in male monkeys, 100 mg/kg/day in female monkeys) was 4.83 times (male rats), 7.06 times (female rats), 5.12 times (male monkeys), and 19.2 times (female monkeys) as the exposure (AUC_t, 1409 ng·h/mL) observed at the clinical dose (5 mg).

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female rats (F344)	p.o.	28 days (once daily)	0,[a] 3, 10, 100, 1000	≥100: Reduced body weight gain, decreased body weight, decreased food consumption, decreased hair follicles and subcutaneous tissue, vacuolation of adrenal glomerulosa cells 1000: Decreased dermis Reversibility: Yes (except vacuolation of adrenal glomerulosa cells)	10	4.2.3.2-1
Male and female rats (F344)	p.o.	3 months (once daily)	0,[a] 3, 10, 30, 100	≥30 (male): Reduced body weight gain, decreased food consumption 100 (female): Reduced body weight gain	10 (male) 30 (female)	4.2.3.2-2
Male and female rats (F344)	p.o.	6 months (once daily)	0,[a] 3, 30, 100	≥30: Reduced body weight gain, decreased food consumption	3	4.2.3.2-3
Male and female cynomolgus monkeys	p.o.	28 days (once daily)	0,[a] 10, 30, 100, 1000	≥100 (female): Decreased body weight, decreased food and water consumption 1000 (male): Decreased body weight Reversibility: Yes	100 (male) 30 (female)	4.2.3.2-4
Male and female cynomolgus monkeys	p.o.	3 months (once daily)	0,[a] 10, 100, 1000	≥100 (female): Decreased body weight 1000 (male): Decreased body weight, emaciation	100 (male) 10 (female)	4.2.3.2-5
Male and female cynomolgus monkeys	p.o.	9 months (once daily)	0,[a] 10, 100, 300	Death[b]: 100 (1/4 males), decreased physical activity, hypothermia, decreased food consumption, decreased body weight 300: Decreased body weight	10 (male) 100 (female)	4.2.3.2-6

a: 0.5% methylcellulose solution
b: Supposedly due to aggravation of clinical signs caused by esaxerenone

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay in Chinese hamster lung (CHL) cells, and *in vivo* genotoxicity studies consisted of a rat bone marrow micronucleus assay were conducted. No genotoxicity was observed (Table 14).

Table 14. Genotoxicity studies

Study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or mmol/L) Dose (mg/kg/day)	Results	CTD
In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	S9 −/+	0,[a] 19.5 (S9 − only), 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000	Negative	4.2.3.3.1-1
		Escherichia coli: WP2*uvrA*				
	Chromosomal aberration assay using cultured mammalian cells	CHL	S9 −/+ (6 hours)	0,[a] 0.105, 0.126, 0.151, 0.181, 0.217 (S9 + only)	Negative	4.2.3.3.1-2
			S9 − (24 hours)	0,[a] 0.0522, 0.0627, 0.0752, 0.0903, 0.108, 0.130, 0.156		
In vivo	Micronucleus assay in rodents	Bone marrow of male and female rats (SD)		0,[b] 500, 1000, 2000	Negative	4.2.3.3.2-1

a: Dimethyl sulfoxide (DMSO)
b: Aqueous 0.5% methylcellulose solution/suspension

5.4 Carcinogenicity

Long-term carcinogenicity studies were conducted in mice and rats. No carcinogenicity was detected (Table 15).

Table 15. Carcinogenicity studies

Test system	Route of administration	Administration period	Main lesions	Dose	(mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	CTD
					0[a]	10	30	100		
				No. of animals	55/sex	55/sex	55/sex	55/sex		
Male and female mice (B6C3F1)	p.o.	2 years (once daily)	Neoplastic lesions		None				100	4.2.3.4.1-3
			Non-neoplastic lesions		Regeneration of renal tubular epithelial cells, hyaline cast, fatty change of the hepatocytes, and aggravation of fibrotic lesions of femur and sternum					
Male and female rats (F344)	p.o.	2 years (once daily)	Main lesions	Dose	(mg/kg/day)				30	4.2.3.4.1-4
					0[a]	3	10	30		
				No. of animals	55/sex	55/sex	55/sex	55/sex		
			Neoplastic lesions		None					
			Non-neoplastic lesions		Aggravation of chronic progressive nephropathy, dilatation of large intestine (cecum, colon, rectum) accompanied by fecal retention					

a: 0.5% methylcellulose solution

5.5 Reproductive and developmental toxicity

The applicant conducted a study of fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a study of effects on pre- and postnatal development, including maternal function in rats (Table 16). Findings in the study of fertility and early embryonic development to implantation in male and female rats included decreased corpora lutea count, decreased number of implantation, decreased number of live embryos, and increased rate of retained placenta. The embryo-fetal development studies did not show teratogenicity. Findings in the studies of effects on pre- and postnatal development, including maternal function in rats included reduced body weight gain or body weight decrease in maternal animals and reduced body weight gain in pups. The exposure to esaxerenone ($AUC_{0\text{-}24}$) at the NOAEL for embryo-fetal development (1000

mg/kg/day in rats, 300 mg/kg/day in rabbits) was 128 times (rats) and 19.1 times (rabbits) as the exposure (AUC_t, 1409 ng·h/mL) at the clinical dose (5 mg).

Table 16. Reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Study of fertility and early embryonic development to implantation	Male and female rats (SD)	p.o.	(male) From 2 weeks before mating to 1 day before necropsy (once daily) (female) From 2 weeks before mating to gestation day 7 (once daily)	0,[a] 10, 30, 100	Parental animals: ≥30 (male), 100 (female): Reduced body weight gain, decreased body weight, decreased food consumption Fertility, early embryogenic development: 100: Decreases in corpora lutea, implantation, and live embryos, increased rate of retained placenta	Parental animals (general toxicity): 10 Parental animals (fertility, early embryonic development): 30	4.2.3.5.1-1
Embryo-fetal development studies	Female rats (SD)	p.o.	Gestation day 7 to 17 (once daily)	0,[a] 100, 300, 1000	Maternal animals: ≥100: Reduced body weight gain, decreased body weight, decreased food consumption	Maternal animals (general toxicity): <100 Embryo-fetal development: 1000	4.2.3.5.2-2
	Female rabbits (NZW)	p.o.	Gestation day 6 to 18 (once daily)	0,[a] 30, 100, 300	Maternal animals: 300: Reduced body weight gain, decreased body weight, decreased food consumption	Maternal animals (general toxicity): 100 Embryo-fetal development: 300	4.2.3.5.2-4
Study of effects on pre- and postnatal development, including maternal function	Female rats (SD)	p.o.	Maternal animals: Gestation day 7 to postpartum day 21 (once daily)	0,[a] 10, 30, 100	Maternal animals: ≥30: Reduced body weight gain, decreased body weight, decreased food consumption F1 offspring: ≥30: Decreased body weight, reduced body weight gain	Maternal animals (general toxicity): 10 Maternal animals (fertility): 100 Development and fertility of F1 offspring: 10	4.2.3.5.3-1

a: 0.5% methylcellulose solution

5.6 Local tolerance

Table 17. Local tolerance study

Test system	Application site	Testing method	Main findings	CTD
Rats (F344)	i.v.	A single dose, 1-hour continuous administration at 0, 0.025, 0.05 mg/mL	None	4.2.3.6-1

5.7 Other toxicity studies

5.7.1 Phototoxicity

Esaxerenone was positive in an *in vitro* phototoxicity study using Balb/c 3T3 mouse fibroblasts, whereas no findings suggestive of phototoxicity were observed in an *in vivo* phototoxicity study using pigmented rats. Therefore, the applicant determined that esaxerenone is unlikely to induce phototoxicity clinically (Table 18).

Table 18. Phototoxicity studies

Test	Test system	Testing method	Main findings	CTD
Phototoxicity studies	Mouse fibroblasts Balb/c 3T3	0, 0.015, 0.046, 0.14, 0.41, 1.2, 3.7, 11, 33, 100 μg/mL UV irradiation	Phototoxicity (photo irritation factor >17)	4.2.3.7.7-1
	Male pigmented rats (Long-Evans)	A single oral administration at 0,[a] 10, 100 mg/kg, followed by UV irradiation with a xenon lamp at 7 hours after administration	None	4.2.3.7.7-2

a: 0.5% methylcellulose solution

5.7.2 Hemolysis test

Table 19. Hemolysis test

Test	Test system	Testing method	Main findings	CTD
Hemolysis test	Human peripheral blood	2.5 mg formulation (0, 0.025, 0.05 mg/mL) was added to 0.5 mL of human blood, and after the mixture was incubated at 37°C for 30 minutes, the absorbance of the supernatant at 540 nm was measured, and the hemolysis rate was calculated from the absorbance.	No hemolytic activity	4.2.3.7.7-3

5.7.3 Impurities

Esaxerenone-related compounds that might induce gene mutation were subjected to a reverse mutation test by referring to “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (ICH M7 Guideline). All of the compounds tested were negative.

Table 20. Genotoxicity tests of impurities

Test substance	Study		Test system	Metabolic activation (treatment)	Concentration (μg/plate)	Results	CTD
Related Substance A	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 19.5-5000	Negative	4.2.3.7.7-9
Related Substance B	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 2.44-625	Negative	4.2.3.7.7-10
Related Substance C	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 156-5000	Negative	4.2.3.7.7-11
Related Substance D	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 156-5000	Negative	4.2.3.7.7-12
Related Substance E	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 9.77-1250	Negative	4.2.3.7.7-13
Related Substance F	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 78.1-5000	Negative	4.2.3.7.7-14
Related Substance G	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 78.1-5000	Negative	4.2.3.7.7-15
Related Substance H	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 156-5000	Negative	4.2.3.7.7-16
Related Substance I	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 156-5000	Negative	4.2.3.7.7-17
Related Substance J	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 4.88-5000	Negative	4.2.3.7.7-18
Related Substance K	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, *Escherichia coli*: WP2*uvrA*	S9 −/+	0,[a] 78.1-5000	Negative	4.2.3.7.7-19

a: DMSO

5.R Outline of the review conducted by PMDA

Based on the reviews on nonclinical toxicity data submitted, PMDA concluded that there is no problem in the clinical use of esaxerenone.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

In the dose-finding study (Study J203) and the Japanese phase III studies (Studies J301, J302, etc.) in patients with essential hypertension, 1.25-, 2.5-, and 5-mg tablet formulations for late phase II/phase III studies were used. In the study on the food effect (Study J112), 5-mg tablet formulation for late phase II/phase III studies was used. The 1.25-, 2.5-, and 5-mg to-be-marketed tablet formulations were [redacted] from the formulations for late phase II/phase III studies, and only 1.25-mg formulation was [redacted]. Bioequivalence (BE) between the formulations for late phase II/phase III studies and the to-be-marketed formulations is demonstrated for each dose strength based on the results of the dissolution tests according to BE Guideline for formulation change. BE of the to-be-marketed formulations between 5-mg tablets and 1.25-mg tablets and between 5 mg-tablets and 2.5-mg tablets is demonstrated by dissolution tests performed according to BE Guideline for different strengths.

Plasma concentrations of esaxerenone and its metabolites R-413942, A200-4164, and A214-4026 were measured by LC-MS/MS, and the lower limit of quantitation was 0.1, 0.05 to 0.1, 0.1, and 0.075 to 0.1 ng/mL, respectively.

Unless otherwise specified, PK parameters are expressed as the mean or mean ± SD.

6.1.1 Absolute bioavailability and study on food effect (Study J112, CTD 5.3.1.1-2)

A six-treatment, three-period crossover study was conducted in 24 healthy adult Japanese men to investigate absolute bioavailability (BA) and the food effect on the PK of esaxerenone (washout period, 8 days).

Following a single intravenous or oral administration of esaxerenone (5 mg), the absolute BA (geometric least squares mean ratio [95% confidence interval (CI)] of AUC_{∞} after oral administration to that after intravenous administration) was 0.890 [0.867, 0.915] after oral administration under fasted conditions and 0.908 [0.883, 0.932] after oral administration under fed conditions. V_{ss} and CL of esaxerenone after intravenous administration were 80.2 ± 9.50 L and 3.69 ± 0.554 L/h, respectively.

Following a single oral administration of esaxerenone (5 mg) under fasted conditions or after meals, the geometric least squares mean ratio [90% CI] of C_{max} and AUC_{last} of esaxerenone after administration under fed conditions to that after administration under fasted conditions was 1.010 [0.951, 1.073] and 1.019 [0.995, 1.042], respectively. Median T_{max} after administration under fasted and fed conditions was 3.00 and 2.50 hours, respectively.

6.2 Clinical pharmacology

Unless otherwise specified, PK parameters are expressed as the mean or mean ± SD.

6.2.1 *In vitro* studies using human biomaterials

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 5.3.2.1-1 and 5.3.2.1-2)

Following the addition of esaxerenone (final concentration, 0.06-6.43 μmol/L) to human plasma, the protein binding was 98.2% to 99.0%.

Following the addition of ^{14}C-esaxerenone (final concentration, 0.06-6.43 μmol/L) to human blood, the distribution rate in blood cells was 28.6% to 30.4%.

6.2.1.2 Metabolism of esaxerenone (CTD 5.3.2.2-1 to 5.3.2.2-3)

Human liver microsomes were incubated with ^{14}C-esaxerenone (final concentration, 5 μmol/L) in the presence of NADPH or UDPGA at 37°C for 2 hours. As a result, A200-5386, A200-7709, and R-413942 were detected in the presence of NADPH and A200-4164 was detected in the presence of UDPGA.

Human cytochrome P450 (CYP) isoform-expressing systems (expressing CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) were incubated with esaxerenone (final concentration, 10 μmol/L) at 37°C. As a result, A200-5386, A200-7709, and R-413942 were formed in CYP3A4- and CYP3A5-expressing systems.

Human uridine 5'-diphosphate-glucuronosyltransferase (UGT) isoform-expressing systems (expressing UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15) were incubated with esaxerenone (final concentration, 10 μmol/L) at 37°C. As a result, A200-4164 was formed in UGT1A1-, UGT1A3-, UGT1A4-, UGT1A9-, UGT2B7-, and UGT2B15-expressing systems.

6.2.1.3 CYP inhibition (CTD 5.3.2.2-4)

Human liver microsomes were incubated with a substrate of each CYP isoform (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) and esaxerenone (final concentration, 0.1-100 μmol/L) at 37°C, and the inhibitory effect of esaxerenone against metabolism of the substrate of each CYP isoform was investigated.

The IC_{50} of esaxerenone against CYP1A2, CYP2A6, CYP2D6, and CYP2E1 was ≥100 μmol/L, and IC_{50} against CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A (substrates, midazolam and testosterone) was 18.5, 49.6, 20.0, 31.4, and 55.1 μmol/L (midazolam) and ≥100 μmol/L (testosterone), respectively. When liver microsomes were pre-incubated with esaxerenone for 30 minutes, esaxerenone did not inhibit CYP2B6, CYP2C8, CYP2C9, or CYP2C19 in a time-dependent manner, whereas IC_{50} of esaxerenone against CYP3A was 14.0 μmol/L (midazolam) and 37.6 μmol/L (testosterone), indicating a time-dependent inhibition .

6.2.1.4 UGT inhibition (CTD 5.3.2.2-5)

Human liver microsomes were incubated with the substrate of each UGT isoform (UGT1A1 and UGT2B7) and esaxerenone (final concentration, 0.1-100 μmol/L) at 37°C, and the inhibitory effect of esaxerenone against the metabolism of the substrate of each UGT isoform was investigated. The IC_{50} of esaxerenone against UGT1A1 was 23.6 μmol/L, and inhibition constant (Ki) was 12.4 μmol/L. The IC_{50} of esaxerenone against UGT2B7 was ≥100 μmol/L.

6.2.1.5 CYP induction (CTD 5.3.2.2-6 and 5.3.2.2-7)

Esaxerenone was incubated with human hepatocytes at 37°C for 72 hours, and enzyme-inducing activity of esaxerenone was investigated. No increase in the expression level of CYP1A2 messenger ribonucleic acid (mRNA) was observed in the presence of esaxerenone (final concentration, 0.1-10 μmol/L). In contrast, when esaxerenone (final concentration, 0.1-30 μmol/L) was added, the expression level of CYP3A4 and CYP2B6 mRNAs increased in an esaxerenone concentration-dependent manner and, in concentration of esaxerenone at ≥3 and ≥10 μmol/L, respectively, reached ≥2 times the level observed in the negative control. The expression level of CYP3A4 and CYP2B6 mRNAs was 25.5 and 4.1 times, respectively, the level observed in the negative control at maximum.

These results showed that esaxerenone induces CYP3A4 and CYP2B6. However, since the exposure (C_{max} 82.4 ng/mL [exposure under steady state in repeated administration of 5 mg of esaxerenone, estimated by population pharmacokinetics (PPK) analysis]) achieved in repeated oral administration of esaxerenone at the recommended clinical dose is far below the level required for CYP2B6 induction, esaxerenone is unlikely to cause drug-drug interaction mediated by CYP2B6 induction.

6.2.1.6 Studies on transporters (CTD 5.3.2.2-8 to 5.3.2.2-10)

When esaxerenone (final concentration, 1 μmol/L) was added to Caco-2 cells, the efflux ratio ("apparent permeability coefficient from basolateral surface to apical surface"/"apparent permeability coefficient from apical surface to basolateral surface" [$P_{app}B \rightarrow A/P_{app}A \rightarrow B$]) of esaxerenone was 2.59. In the presence of verapamil (a P-glycoprotein [P-gp] inhibitor), novobiocin (a breast cancer resistance protein [BCRP] inhibitor), or GF120918 (a P-gp and BCRP inhibitor), the efflux ratio of esaxerenone was 0.94, 1.68, and 0.73, respectively.

Using MDCK-II cells expressing a human transporter (organic anion transporter [OAT]1, OAT3, organic cation transporter [OCT]1, OCT2, organic anion transporting polypeptide [OATP]1B1, or OATP1B3), the inhibitory effect of esaxerenone (final concentration, 0.1-30 μmol/L) against the typical substrate of each transporter was investigated. IC_{50} of esaxerenone against OCT1 was 9.84 μmol/L, whereas IC_{50} of esaxerenone against OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 was ≥30 μmol/L.

Using Caco-2 cells, the inhibitory effect of esaxerenone (final concentration, 0.1-30 μmol/L) against transcellular transport of the typical substrate of P-gp and BCRP was investigated. The IC_{50} of esaxerenone was 16.3 and 24.6 μmol/L, respectively.

Using HEK293 cells expressing human multidrug and toxin extrusion (MATE) 1 or MATE2-K, the inhibitory effect of esaxerenone (final concentration, 0.3-100 μmol/L) against intracellular uptake of the typical substrate of MATE1 and MATE2-K was investigated. IC_{50} of esaxerenone was 9.70 and 5.64 μmol/L, respectively.

6.2.2 Studies in healthy adults

6.2.2.1 Phase I single-dose administration study (Study CS3150-A-J101, CTD 5.3.3.1-1)

Table 21 shows PK parameters of esaxerenone following a single oral administration of esaxerenone (5-200 mg) to healthy adult Japanese men under fasted conditions.

Table 21. PK parameters of esaxerenone following a single oral administration of esaxerenone under fasted conditions

Dose (mg)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)
5	66.33 ± 7.9056	3.50	1296 ± 148.85	19.73 ± 4.4797
10	128.8 ± 25.957	3.50	2455 ± 525.21	18.73 ± 2.2294
20	415.0 ± 176.70	2.50	6895± 1546.7	22.19 ± 3.2572
50	559.2 ± 74.478	2.75	12,710 ±1985.2	21.85 ± 4.4463
100	920.0 ± 151.82	2.50	20,510 ± 3881.7	22.85 ± 3.3363
200	1662 ± 329.99	3.00	46,390 ± 10,168	20.60 ± 1.7287

n = 6/group
a: Median

6.2.2.2 Phase I multiple-dose administration study (Study CS3150-A-J102, CTD 5.3.3.1-2)

Table 22 shows PK parameters of esaxerenone in once-daily oral administration of esaxerenone (10-100 mg) for 10 days to healthy adult Japanese men under fasted conditions.

Table 22. PK parameters of esaxerenone in once-daily oral administration of esaxerenone for 10 days under fasted conditions

Dose (mg)	Day of administration	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{τ} (ng·h/mL)	$t_{1/2}$ (h)
10	Day 1	161.9 ± 25.903	2.50	1722 ± 210.10	—
	Day 10	174.4 ± 27.694[b]	2.50 [b]	2353 ± 511.32 [b]	25.05 ± 5.4481 [b]
20	Day 1	220.5 ± 34.801	2.50	2651 ± 455.37	—
	Day 10	393.4 ± 78.780	3.00	5224 ± 1117.4	24.21 ± 6.3137
50	Day 1	489.5 ± 134.83	3.75	6294 ± 1168.3	—
	Day 10	744.8 ± 125.93	2.75	10,520 ± 1258.8	22.39 ± 2.4903
100	Day 1	858.6 ± 196.32	2.50	11,300 ± 1816.6	—
	Day 10	1416 ± 326.58	3.50	20,170 ± 3966.9	22.32 ± 4.4154 [b]

n = 8/group
—: Not calculated
a: Median
b: Data of 7 subjects

6.2.2.3 Mass balance study (Study CS3150-A-U105, CTD 5.3.2.3-1, 5.3.2.3-2, and 5.3.3.1-3 [Reference data])

Following a single oral administration of ^{14}C-esaxerenone (20 mg) to 6 healthy adult non-Japanese men under fasted conditions, median t_{max} of radioactivity in whole blood and in plasma was 3.25 and 3.75 hours, respectively, C_{max} was 281 ± 39.2 and 430 ± 65.3 ng eq./mL, respectively, AUC_{last} was 7880 ± 1210 and 12,600 ± 2100 h·ng eq./mL, respectively, and $t_{1/2}$ was 29.6 ± 4.92 and 30.8 ± 3.95 hours, respectively. Table 23 shows the PK parameters of esaxerenone and its metabolites (R-413942, A200-4164, and A214-4026) in plasma.

Urinary and fecal excretion rates of radioactivity (percentage relative to the administered radioactivity) up to 168 hours after administration were 38.0% ± 4.94% and 51.0% ± 9.35%, respectively. The unchanged esaxerenone was scarcely excreted (1.6%) in urine up to 72 hours after administration, and mainly A214-4026 (10.5%), A200-4164 (7.2%), and A200-7709 (2.6%) were detected. In contrast, the

unchanged esaxerenone was excreted to a substantial extent (18.7%) into feces within 168 hours after administration, together with metabolites A200-5386/A200-7449 (10.1%; sum of A200-5386 and A200-7449 because they could not be measured separately from each other) and A200-7709 (9.0%), among others.

Table 23. PK parameters of esaxerenone and main metabolites

	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	Ratio of AUC_{∞} relative to that in total radioactivity in plasma (%)
Esaxerenone	237 ± 59.7	2.25	5310 ± 1390	34.0 ± 9.82	3.96 ± 0.944	187 ± 36.0	40.8 ± 5.71
R-413942	1.00 ± 0.297	48.03	198 ± 57.0	NC	—	—	1.75 ± 0.609
A200-4164	165 ± 39.7	4.00	3860 ± 1190	27.8 ± 12.9	—	—	21.4 ± 4.23
A214-4026	39.0 ± 2.87	3.75	1060 ± 72.2	26.4 ± 10.2	—	—	7.97 ± 0.818

Not calculated
—: Not applicable
*: Median

6.2.3 Studies in patients

6.2.3.1 Phase II dose exploration study in patients with essential hypertension (Study CS3150-A-J201, CTD 5.3.5.1-3)

Esaxerenone 1.25, 2.5, 5, or 10 mg was administered once daily after breakfast for 6 weeks to 164 patients with essential hypertension. On Day 1 of administration, C_{max} of esaxerenone in the 1.25, 2.5, 5, and 10 mg groups was 13.38 ± 2.8290, 30.97 ± 6.5394, 58.89 ± 13.372, and 116.6 ± 29.210 ng/mL, respectively, and $AUC_{0\text{-}24}$ was 181.5 ± 30.531, 404.7 ± 102.82, 803.5 ± 159.17, and 1502 ± 314.29 ng·h/mL, respectively. Median T_{max} was 3.00 hours in all groups. The trough plasma concentration of esaxerenone reached roughly the steady state on Day 7 of administration. At 24 hours after the last dose, the trough plasma concentration of esaxerenone in the 1.25, 2.5, 5, and 10 mg groups was 8.066 ± 1.8054, 19.49 ± 7.6128, 39.39 ± 13.403, and 68.16 ± 15.246 ng/mL, respectively.

6.2.3.2 Phase II dose-finding study in patients with essential hypertension (Study CS3150-A-J203, CTD 5.3.5.1-1)

Esaxerenone 1.25, 2.5, or 5 mg was administered once daily after breakfast for 12 weeks to 426 patients with essential hypertension. At Week 12 of administration, the plasma trough concentration of esaxerenone in the 1.25, 2.5, and 5 mg groups was 8.673 ± 2.8673, 15.72 ± 6.7429, and 32.74 ± 15.547 ng/mL, respectively.

6.2.3.3 Phase III study in patients with essential hypertension (Study CS3150-A-J301, CTD 5.3.5.1-2)

Esaxerenone 2.5 or 5 mg was administered once daily after breakfast for 12 weeks to 1001 patients with essential hypertension. At Week 12 of administration, the trough plasma concentration of esaxerenone in the 2.5 and 5 mg groups was 15.8 ± 6.48 and 32.0 ± 13.0 ng/mL, respectively.

6.2.3.4 Phase II study in hypertensive patients with moderate renal impairment (Study CS3150-A-J206, CTD 5.3.5.2-5)

Pharmacokinetics of esaxerenone was investigated in 33 hypertensive Japanese patients with moderate renal impairment (estimated glomerular filtration rate [eGFR], ≥30 mL/min/1.73 m^2 and

<60 mL/min/1.73 m^2) receiving esaxerenone orally once daily after breakfast for 12 weeks. The starting dose of esaxerenone was 1.25 mg, and a dose increase to 2.5 mg was allowed either at Week 4 or Week 8 of administration at the discretion of the investigator or the subinvestigator. Only subjects who increased the dose to 2.5 mg at Week 4 were allowed to increase the dose to 5 mg at Week 8 at the discretion of the investigator or the subinvestigator.

The dose was increased to 2.5 mg in all subjects at Week 4 and to 5 mg in 30 subjects at Week 8.

On Day 1 of administration of esaxerenone 1.25 mg, PK parameters were as follows: C_{max} was 14.74 ± 2.7378 ng/mL, AUC_{0-24} was 193.3 ± 33.958 ng·h/mL, and median T_{max} was 3.00 hours. Table 24 shows trough plasma concentrations of esaxerenone at Week 2 to 12 of administration.

Table 24. Trough plasma concentration of esaxerenone at Week 2 to 12 of administration

	Esaxerenone dose (mg)	Trough plasma concentration of esaxerenone (ng/mL)
Week 2	1.25	10.24 ± 2.5932 (30)
Week 4	1.25	9.596 ± 2.4801 (30)
Week 8	2.5	19.12 ± 6.1023 (26)
Week 12	5	41.02 ± 12.227 (27)

(Number of subjects)

6.2.3.5 Phase III study in hypertensive patients with moderate renal impairment (Study CS3150-A-J305, CTD 5.3.5.2-4)

Pharmacokinetics of esaxerenone was investigated in 58 Japanese hypertensive patients with moderate renal impairment (eGFR, ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) receiving esaxerenone orally once daily after breakfast for 12 weeks in combination with an angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor. The starting dose of esaxerenone was 1.25 mg, and the dose was allowed to be increased to 2.5 mg either at Week 4, 6, or 8 of administration at the discretion of the investigator or the subinvestigator. Only subjects who increased the dose to 2.5 mg at Week 4 were allowed to increase the dose to 5 mg at Week 8 at the discretion of the investigator or the subinvestigator.

The trough plasma concentration of esaxerenone in subjects receiving 1.25, 2.5, or 5 mg of esaxerenone at Week 12 was 12.7 ± 4.72 (4 subjects), 18.3 ± 7.69 (26 subjects), and 36.9 ± 10.8 ng/mL (25 subjects), respectively.

6.2.3.6 Phase III study in hypertensive patients with type 2 diabetes mellitus and albuminuria (Study CS3150-A-J306, CTD 5.3.5.2-6)

Esaxerenone was administered to 51 Japanese hypertensive patients with type 2 diabetes mellitus and albuminuria once daily after breakfast for 12 weeks in combination with an ARB or ACE inhibitor. The starting dose of esaxerenone was 1.25 mg, and the dose was allowed to be increased to 2.5 mg either at Week 4, 6, or 8 of administration at the discretion of the investigator or the subinvestigator. Only subjects who increased the dose to 2.5 mg at Week 4 were allowed to increase the dose to 5 mg at Week 8 at the discretion of the investigator or the subinvestigator.

The trough plasma concentration of esaxerenone in subjects receiving 1.25, 2.5, or 5 mg of esaxerenone at Week 12 was 10.1 ± 3.86 (6 subjects), 15.3 ± 6.23 (22 subjects), and 33.9 ± 14.5 ng/mL (18 subjects), respectively.

6.2.4 Studies of intrinsic factors

6.2.4.1 Study in patients with hepatic impairment (Study CS3150-A-J109, CTD 5.3.3.3-1)

A single dose of esaxerenone 2.5 mg was administered after meals to 6 each of healthy Japanese adults, patients with mild hepatic impairment (Child-Pugh class A), and patients with moderate hepatic impairment (Child-Pugh class B). The geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] in patients with mild hepatic impairment to that in healthy adults was 0.959 [0.778, 1.182] and 0.837 [0.637, 1.099], respectively, and the geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] in patients with moderate hepatic impairment to that in healthy adults was 0.804 [0.653, 0.992] and 1.078 [0.820, 1.415], respectively.

6.2.5 Drug interaction studies

6.2.5.1 Midazolam (Study CS3150-A-J107, CTD 5.3.3.4-1)

The effect of esaxerenone on PK of midazolam was investigated in 28 healthy Japanese adults. On Day 1, midazolam (2 mg) alone was administered orally in a single dose. From Day 2 through 14, esaxerenone (5 mg) alone was administered orally once daily. On Day 15, esaxerenone (5 mg) and midazolam (2 mg) were administered in combination. The drugs were administered under fasted conditions on Day 1, 2, and 15, and after meals on other treatment days. The geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] of midazolam in combination with esaxerenone to that in midazolam monotherapy was 1.224 [1.116, 1.342] and 1.201 [1.110, 1.300], respectively.

6.2.5.2 Itraconazole (Study CS3150-A-J108, CTD 5.3.3.4-2)

The effect of itraconazole on PK of esaxerenone was investigated in 20 healthy Japanese adults. A single dose of esaxerenone (2.5 mg) alone was administered orally on Day 1, followed by a withdrawal period until Day 7. On Day 8, itraconazole (200 mg) was administered twice daily and, from Day 9 through 16, itraconazole (200 mg) was administered orally once daily. On Day 13, esaxerenone (2.5 mg) and itraconazole (200 mg) were concomitantly administered. The drugs were administered under fasted conditions on Day 1 and 13 and after meals on other treatment days.

The geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] of esaxerenone in combination with itraconazole to that in esaxerenone monotherapy was 1.126 [1.054, 1.202] and 1.468 [1.399, 1.541], respectively.

6.2.5.3 Amlodipine (Study CS3150-A-J110, CTD 5.3.3.4-3)

The effect of amlodipine on PK of esaxerenone was investigated in 24 healthy Japanese adults. A single dose of esaxerenone (2.5 mg) alone was administered orally on Day 1, followed by a withdrawal period until Day 7. On Day 8 through 18, amlodipine (10 mg) was administered orally once daily, and esaxerenone (2.5 mg) and amlodipine (10 mg) were concomitantly administered on Day 15. The drugs were administered under fasted conditions on Day 1 and 15 and after meals on other treatment days.

The geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] of esaxerenone in combination with amlodipine to that in esaxerenone monotherapy was 0.958 [0.905, 1.015] and 1.154 [1.118, 1.190], respectively.

The effect of esaxerenone on PK of amlodipine was investigated in 20 healthy Japanese adults. A single dose of amlodipine (2.5 mg) alone was administered orally after breakfast on Day 1, followed by a withdrawal period until Day 7. On Day 8 through 25, esaxerenone (5 mg) was administered orally once daily after breakfast, and esaxerenone (5 mg) and amlodipine (2.5 mg) were concomitantly administered on Day 21.

The geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] of amlodipine in combination with esaxerenone to that in amlodipine monotherapy was 1.099 [1.059, 1.140] and 1.185 [1.132, 1.240], respectively.

6.2.5.4 Digoxin, rifampicin (Study CS3150-A-J111, CTD 5.3.3.4-4)

The effect of esaxerenone on PK of digoxin under steady state was investigated in 20 healthy Japanese adults. Digoxin (0.25 mg) was administered orally once daily after breakfast from Day 1 through 10, and digoxin (0.25 mg) and esaxerenone (5 mg) were concomitantly administered once daily after breakfast from Day 11 through 15.

The geometric least squares mean ratio of C_{max}, $C_{trough,}$, and AUC_t [90% CI] of digoxin in combination with esaxerenone to that in digoxin monotherapy was 1.130 [0.998, 1.280], 1.088 [1.033, 1.145], and 1.072 [1.015, 1.133], respectively.

The effect of rifampicin on PK of esaxerenone was investigated in 12 healthy Japanese adults. A single dose of esaxerenone (5 mg) alone was administered orally on Day 1, followed by a withdrawal period until Day 7. From Day 8 through 16, rifampicin (600 mg) was administered orally once daily after breakfast and, on Day 13, a single dose of esaxerenone (5 mg) was administered orally at 2 hours after administration of rifampicin (600 mg). On Day 1 and 13, esaxerenone was administered under fasted conditions.

The geometric least squares mean ratio of C_{max} and AUC_{last} [90% CI] of esaxerenone in combination with rifampicin to that in esaxerenone monotherapy was 0.659 [0.599, 0.724] and 0.315 [0.300, 0.332], respectively.

6.2.6 PPK analysis and PPK/pharmacodynamics (PD) analysis

6.2.6.1 PPK analysis (CTD 5.3.3.5-1 [reference data])

PPK analysis was performed using the data of 15 clinical studies (Studies J101, J102, J108, J109, J110, J111, J112, J201, J202, J203, J204, J206, J301, J305, and J306). Plasma esaxerenone concentration data at 8263 measuring points obtained from 1623 subjects were used as the data set for analysis.

In PPK analysis, a 3-compartment model with continuous zero- and first-order processes and with first-order elimination was selected as the structural model. An exponential error model was selected for both

the inter-individual variability error model and residual error model for PK parameters. Since itraconazole and rifampicin clearly affected the PK of esaxerenone, their concomitant use was included as covariates for CL and F in the basic model in advance. Also, as esaxerenone absorption reached a plateau at ≥50 mg, the dose of ≥50 mg was included as a covariate for F in advance in the basic model. As possible covariates for PK of esaxerenone, the following parameters were selected: Disease condition (1097 patients with hypertension, 360 patients with diabetic nephropathy [DN], 166 healthy subjects), sex (1239 men, 384 women), smoking habit (357 smokers, 1266 nonsmokers), potent CYP3A inhibitor (66 users, 1557 nonusers), potent CYP3A inducers (1 user, 1622 nonusers), age (median [min, max]) (58 [20, 87] years), body weight (67.8 [34.5, 136] kg), alkaline phosphatase (ALP) (209 [71.0, 474] U/L), alanine aminotransferase (ALT) (20 [6.0, 97] U/L), aspartate aminotransferase (AST) (23 [10, 180] U/L), total bilirubin (T-BIL) (0.8 [0.2, 2.8] mg/dL), γ-glutamyl transferase [γ-GTP] (29.0 [7.00, 961] U/L), and eGFR (75.5 [35.0, 149] mL/min/1.73 m^2).

As a result, body weight, age, eGFR, smoking habit, and AST were identified as covariates for CL, and body weight and age as covariates for V_c in the final model.

The effect of the identified covariates on AUC_{ss} of esaxerenone was investigated. Compared with typical subjects (58 years old, 68 kg, eGFR 75 mL/min/1.73 m^2, AST 23 IU/L, nonsmokers, use without itraconazole, use without rifampicin), AUC_{ss} of esaxerenone was estimated to be higher by 1.64-fold in itraconazole users, 0.32-fold in rifampicin users, 1.36-fold in subjects weighing 40 kg, and 0.72-fold in subjects weighing 120 kg. The effect of age, eGFR, smoking habit, and AST on AUC_{ss} of esaxerenone was minimal. The analysis of the final model suggested that inter-individual variability of CL and V_c of esaxerenone was minimal (approximately 18% and 17%, respectively, in coefficient of variation), whereas the interindividual variation of the absorption rate constant (ka) and zero-order absorption time was estimated to be large (approximately 45% and 78%, respectively, in coefficient of variation).

6.2.6.2 Exposure-response analysis on efficacy (CTD 5.3.3.5-1 [Reference data])

An exposure-response analysis was conducted, using (1) AUC_{ss} obtained from the above PPK analysis [see Section "6.2.6.1 PPK analysis"] based on individual post hoc estimate as the index for exposure, and (2) change from baseline in sitting blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) to Week 12 as the index for efficacy. Data of Studies J203 and J301 were used for the analysis. The analysis data set was SBP and DBP at Week 12 obtained from 991 subjects (332 subjects in Study J203 [85 in the placebo group, 82 in the 1.25 mg group, 80 in the 2.5 mg group, 85 in the 5 mg group], 659 subjects in Study J301 [325 in the 2.5 mg group, 334 in the 5 mg group]). The eplerenone group in Study J301 was excluded from the analysis.

The relationship between AUC_{ss} and SBP as well as between AUC_{ss} and DBP was analyzed using a linear model.

In the basic model, the between-study difference was included in the intercept of the linear regression line by taking into account the difference in the antihypertensive effect between the studies. As possible covariates, the following parameters were investigated: Sex (713 men, 278 women), prior treatment with hypotensive drug (519 subjects with treatment, 472 subjects without treatment), diabetes mellitus (131

subjects with the disease, 860 subjects without the disease), obesity (497 obese, 494 non-obese), age (median [min, max]) (55 [20, 87] years), HbA1c (5.5 [4.5, 8.1]%), eGFR (77.2 [60.0, 141] mL/min/1.73 m^2), baseline SBP (155 [139, 179] mmHg), baseline DBP (96 [89, 109] mmHg), plasma renin activity (PRA) (0.60 [0.05, 8.1] ng/mL/h), and plasma aldosterone concentration (PAC) (108 [9.0, 394] pg/mL). As a result, sex, age, prior treatment with hypotensive drug, baseline SBP, and PRA were identified as the covariates for the exposure-response relationship on SBP, and sex, age, prior treatment with hypotensive drug, baseline DBP, and PAC were identified as the covariates for the exposure-response relationship on DBP.

For both SBP and DBP, the antihypertensive effect of 2.5 mg of esaxerenone was observed in all subpopulations. Investigation of the effect of covariates on the SBP-lowering effect showed that, compared with the typical subjects (men, 55 years old, 70 kg, eGFR 77 mL/min/1.73 m^2, AST 24 IU/L, baseline SBP 155 mmHg, PRA 0.6 ng/mL/h, no smoking habit, use without itraconazole, use without rifampicin), the SBP-lowering effect of esaxerenone was greater by 1.59-fold in women, 1.32- and 0.81-fold, respectively, in subjects aged 80 and 40 years, 0.69-fold in subjects with prior treatment with hypotensive drug, 1.40- and 0.76-fold, respectively, in subjects with baseline SBP of 180 and 140 mmHg, 1.03- and 0.72-fold, respectively, in subjects with baseline PRA of 0.2 and 4 ng/mL/h, 1.17- and 0.88-fold, respectively, in subjects with body weight of 40 and 120 kg, 1.28-fold in itraconazole users, and 0.70-fold in rifampicin users. Investigation of the effect of covariates on the DBP-lowering effect showed that, compared with the typical subjects (men, 55 years old, 70 kg, eGFR 77 mL/min/1.73 m^2, AST 24 IU/L, baseline DBP 96 mmHg, PAC 108 pg/mL, no smoking habit, use without itraconazole, use without rifampicin), the DBP-lowering effect of esaxerenone was greater by 1.53-fold in women, 1.36- and 0.78-fold, respectively, in subjects aged 80 and 40 years, 0.58-fold in subjects with prior treatment with hypotensive drug, 0.85- and 1.34-fold, respectively, in subjects with baseline DBP of 90 and 110 mmHg, 1.08- and 0.85-fold, respectively, in subjects with baseline PAC of 60 and 200 pg/mL, 1.17- and 0.88-fold, respectively, in subjects with body weight of 40 and 120 kg, 1.28-fold in itraconazole users, and 0.70-fold in rifampicin users.

6.2.6.3 Exposure-response analysis on safety (CTD 5.3.3.5-1 [Reference data])

An exposure-response analysis was conducted, using (1) C_{avSS} of esaxerenone (mean plasma esaxerenone concentration up to the first occurrence of the event [serum potassium level ≥5.5 mEq/L] or until the end of administration) obtained from the above PPK analysis [see Section "6.2.6.1 PPK analysis"] based on individual post hoc estimate as the index for exposure and (2) time to the first occurrence of the event as the index for safety. Data of Studies J204, J305, and J306 were used for the analysis. The analysis data set included 462 subjects (353 in J204 [fixed dose], 58 in J305 [optional upward titration], 51 in J306 [optional upward titration]) and 45 subjects (36 in J204, 7 in J305, 2 in J306) experienced the event.

In this analysis, Cox proportional hazard regression was conducted for each of Studies J204, J305, and J306. As possible covariates, the following parameters were selected: Sex (362 men, 100 women), prior treatment with hypotensive drug (462 subjects with treatment, 0 subjects without treatment), diabetes mellitus (417 subjects with the disease, 45 subjects without the disease), age (median [min, max]) (67 [38, 87] years), eGFR (63.3 [34.4, 149] mL/min/1.73 m^2), baseline serum potassium level (4.2 [3.5, 5.0]

mEq/L), HbA1c (6.7 [5.0, 8.3]%), baseline SBP (141 [111, 180] mmHg), baseline DBP (79 [54, 108] mmHg), PRA (1.6 [0.1, 65.9] ng/mL/h), and PAC (79.5 [11, 288] pg/mL).

As a result of the covariate exploration, eGFR and baseline serum potassium level were incorporated into the final model. eGFR was an effect modifier of C_{avSS}. Both in fixed dose (5 mg) administration and in the optional titration (1.25-5 mg), it was suggested that the risk of event increased with decrease in eGFR and increase in baseline serum potassium level. Using the final model, the incidence of event in subjects with eGFR of 66 mL/min/1.73 m^2 and baseline serum potassium level of 4.3 mEq/mL was estimated. As a result, the incidence was approximately 18% in fixed dose administration and 2% in optional titration. It was also suggested that the event risk in optional titration is lower than in fixed dose administration regardless of the combination of eGFR and baseline serum potassium level. In addition, since PPK analysis showed that combination with itraconazole is the extrinsic factor that has the greatest effect on the AUC_{ss} of esaxerenone, the effect of combination with itraconazole on the risk of event was investigated. The risk of event was estimated in typical subjects (55 years old, 70 kg, eGFR 77 mL/min/1.73 m^2, AST 24 IU/L, no smoking habit, without use of rifampicin, baseline serum potassium 4.2 mEq/L) in combination with and without itraconazole. Results suggested that combination with itraconazole had little effect on the risk of event at 1.25 and 2.5 mg of esaxerenone and slightly increased the risk of event at 5 mg of esaxerenone.

6.2.7 QT evaluation study (CTD 5.3.4.1-1)

A four-treatment, four-period cross-over study was conducted to investigate the effect of esaxerenone on QT interval in 55 healthy non-Japanese adults treated with a single dose of placebo, moxifloxacin 400 mg, or esaxerenone 10 or 40 mg under fasted conditions.

C_{max} of esaxerenone in the esaxerenone 10 and 40 mg groups was 108 ± 22.6 and 382 ± 81.1 ng/mL, respectively, AUC_{∞} was 2500 ± 569 and 9630 ± 2200 ng·h/mL, respectively, and median t_{max} was 3.02 and 3.58 hours, respectively.

The lower limit of 90% CI of the difference in the least squares mean of change from baseline in QTcF (QT interval corrected by Fridericia's formula) between subjects receiving moxifloxacin and subjects receiving placebo exceeded 5 ms at 3 measuring timepoints defined in advance. The point estimate of the difference in the least squares mean of change from baseline in QTcF between subjects receiving esaxerenone 10 or 40 mg and subjects receiving placebo was −3.4 to 0.8 ms, with the upper limit of 90% CI being less than 10 ms at all measuring timepoints.

6.R Outline of the review conducted by PMDA

PMDA concluded that although the precautionary statement for patients with hepatic impairment should be discussed further in Section 7.R.3.7, the precautions described in the proposed package insert are appropriate from the stand point of clinical pharmacology, given the submitted study results and the applicant's explanation.

6.R.1 Administration to patients with hepatic impairment

The applicant's explanation about administration of esaxerenone to patients with hepatic impairment:
Following the administration of esaxerenone to healthy adults, patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, C_{max} and AUC_{last} of esaxerenone were similar regardless of the severity of hepatic impairment [see Section "6.2.4.1 Study in patients with hepatic impairment"]. Investigation of the relationship between CL/F of esaxerenone and baseline values of albumin, AST, ALT, ALP, T-BIL, and Child-Pugh score (only in the hepatic impairment group) as hepatic function-related parameters, did not reveal any clear relationship for any of these parameters. In PPK analysis, the effect of AST on the exposure to esaxerenone was investigated. Results showed that AUC_{ss} increased by approximately 5% in patients with AST of 60 IU/L compared with the level in patients with AST of 23 IU/L (median value in the analysis population).

The results of the above clinical study suggest that there is no clear difference in PK of esaxerenone between healthy adults and patients with mild or moderate hepatic impairment. On the other hand, (1) there is no use experience in patients with severe hepatic impairment and (2) studies on metabolism and excretion of esaxerenone suggest that esaxerenone is mainly eliminated by hepatic metabolism, possibly increasing the exposure to esaxerenone in patients with severe hepatic impairment. Therefore, it is considered appropriate to raise caution in administering esaxerenone in patients with severe hepatic impairment in the package insert.

PMDA's view:
Judging from the submitted study results, the applicant's explanation that there is no clear difference in PK of esaxerenone between healthy adults and patients with mild to moderate hepatic impairment is acceptable. Since no clinical study was conducted on patients with severe hepatic impairment, the impact of severe hepatic impairment on the PK of esaxerenone is unknown, thus appropriate precaution should be given in administering esaxerenone to patients with severe hepatic impairment, as proposed by the applicant. The details of the precautionary statement for patients with hepatic impairment should be finalized, also taking account of the results of clinical studies [see Section "7.R.3.7 Treatment with esaxerenone in patients with hepatic impairment"].

6.R.2 Pharmacokinetic interactions with potent CYP3A inhibitors or inducers

The applicant's explanation about the concomitant use with a potent CYP3A inhibitor or inducer on the PK, efficacy, and safety of esaxerenone:
Following the concomitant use of esaxerenone with a potent CYP3A inhibitor itraconazole, C_{max} and AUC_{last} of esaxerenone increased by 1.1- and 1.5-fold, respectively, compared with those in esaxerenone monotherapy [see Section "6.2.5.2 Itraconazole"]. On the other hand, in Studies J302, J305, and J306, adverse events did not show any tendency of increased occurrences during the period of concomitant use with the potent CYP3A inhibitor in 30 subjects who received a potent CYP3A inhibitor and esaxerenone. However, results of the exposure-response analysis on safety predicted a slight increase in the event (serum potassium ≥5.5 mEq/L) in concomitant use of esaxerenone 5 mg with itraconazole [see Section "6.2.6.3 Exposure-response analysis on safety"]. These results suggest that although it is unnecessary to reduce the dose of esaxerenone in all patients in concomitant use with a potent CYP3A inhibitor, cautionary statement should be included in the package insert regarding the concomitant use

with a potent CYP3A inhibitor, taking account of the possible increase in serum potassium level induced by increased plasma esaxerenone concentration.

Following the concomitant use of esaxerenone with a potent CYP3A inducer rifampicin, C_{max} and AUC_{last} of esaxerenone decreased by 0.66- and 0.32-fold, respectively, compared with those in esaxerenone monotherapy [see Section "6.2.5.4 Digoxin, rifampicin"]. Also, results of the exposure-response analysis on efficacy suggested that the antihypertensive effect of esaxerenone was attenuated to 0.70 times that achieved by esaxerenone monotherapy [see Section "6.2.6.2 Exposure-response analysis on efficacy"]. These results suggest the possibility that concomitant use of esaxerenone with a potent CYP3A inhibitor would attenuate the antihypertensive effect due to decreased plasma esaxerenone concentration. Caution should therefore be provided in the package insert to avoid concomitant use with a potent CYP3A inducer whenever possible.

PMDA concluded that the applicant's explanation was appropriate and accepted the proposed precautionary statement in the package insert regarding the concomitant use of esaxerenone with a potent CYP3A inhibitor or inducer.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data from 7 clinical studies shown in Table 25 (for PK, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA").

Table 25. Outline of main clinical studies

Data category	Region	Study	Phase	Study population	Number of enrollments	Outline of dosage regimen	Main endpoints
Evaluation	Japan	J101	I	Healthy adults	Placebo: 12 subjects Esaxerenone 5 mg: 6 subjects Esaxerenone 10 mg: 6 subjects Esaxerenone 20 mg: 6 subjects Esaxerenone 50 mg: 6 subjects Esaxerenone 100 mg: 6 subjects Esaxerenone 200 mg: 6 subjects	Placebo or esaxerenone (5, 10, 20, 50, 100, or 200 mg) was administered as a single dose.	Safety PK
		J102	I	Healthy adults	Placebo: 8 subjects Esaxerenone 10 mg: 8 subjects Esaxerenone 20 mg: 8 subjects Esaxerenone 50 mg: 8 subjects Esaxerenone 100 mg: 8 subjects	Placebo or esaxerenone (10, 20, 50, or 100 mg) was administered once daily repeatedly.	Safety PK
		J203	II	Patients with essential hypertension	Placebo: 87 subjects Esaxerenone 1.25 mg: 83 subjects Esaxerenone 2.5 mg: 84 subjects Esaxerenone 5 mg: 88 subjects Eplerenone: 84 subjects	Placebo, esaxerenone (1.25, 2.5, or 5 mg), or eplerenone (50 mg, increased to 100 mg at Week 2 or 4) was administered once daily orally.	Efficacy Safety
		J301	III	Patients with essential hypertension	Esaxerenone 2.5 mg: 331 subjects Esaxerenone 5 mg: 338 subjects Eplerenone: 332 subjects	Esaxerenone (2.5 mg) or eplerenone (50 mg) was administered once daily orally.	Efficacy Safety
		J302	III	Patients with essential hypertension	Esaxerenone 2.5-5 mg: 368 subjects	Esaxerenone (2.5-5 mg) was administered once daily orally.	Efficacy Safety
		J305	III	Hypertensive patients with moderate renal impairment	Esaxerenone 1.25-5 mg: 58 subjects	Esaxerenone (1.25-5 mg) was administered once daily orally.	Efficacy Safety
		J306	III	Hypertensive patients with type 2 diabetes mellitus and albuminuria	Esaxerenone 1.25-5 mg: 51 subjects	Esaxerenone (1.25-5 mg) was administered once daily orally.	Efficacy Safety

7.1 Phase I studies

7.1.1 Phase I single-dose study (Study CS3150-A-J101, CTD 5.3.3.1-1; Study period, December 2010 to [redacted] 2011)

A randomized, double-blind study was conducted to investigate the safety, pharmacokinetics, and pharmacodynamics of single dose of esaxerenone in 48 healthy Japanese adults (12 subjects in placebo group, 6 subjects in each esaxerenone group) at a Japanese study site. In this study, a single dose of esaxerenone (5, 10, 20, 50, 100, or 200 mg) or placebo was administered orally.

All of the 48 subjects receiving the study drug were included in the safety analysis population.

Adverse events were observed in 4 subjects (2 subjects in the placebo group, 1 subject in the esaxerenone 20 mg group, 1 subject in the esaxerenone 200 mg group). There were neither deaths nor serious adverse events.

There were no adverse events leading to discontinuation of the study drug.

7.1.2 Phase I multiple-dose study (Study CS3150-A-J102, CTD 5.3.3.1-2; Study period, July 2011 to [redacted])

A randomized, double-blind study was conducted to investigate the safety, pharmacokinetics, and pharmacodynamics of multiple dose of esaxerenone in 40 healthy Japanese adults (8 subjects per group) at a Japanese study site. In this study, multiple oral dose of esaxerenone (10, 20, 50, or 100 mg) or placebo was administered.

All of the 40 subjects receiving the study drug were included in the safety analysis population.

Adverse events were observed in 12 subjects (2 subjects in the esaxerenone 10 mg group, 3 subjects in the esaxerenone 20 mg group, 1 subject in the esaxerenone 50 mg group, 6 subjects in the esaxerenone 100 mg group). There were no deaths or serious adverse events.

An adverse event leading to discontinuation of the study drug was observed in 1 subject in the esaxerenone 10 mg group (gastroenteritis).

7.2 Phase II study

7.2.1 Phase II dose-finding study in patients with essential hypertension (Study CS3150-A-J203, CTD 5.3.5.1-1; Study period, January 2015 to September 2015)

A randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of esaxerenone 1.25, 2.5, or 5 mg in patients with essential hypertension (target sample size, 400 subjects in total [80 per group]) at 19 study sites in Japan.

The placebo was administered during the 4-week observation period. During the subsequent 12-week treatment period, placebo, esaxerenone 1.25, 2.5, or 5 mg or eplerenone 50 mg (an open-label comparator, the dose was allowed to be increased to 100 mg at Week 2 or 4) was administered orally once daily. Administration of hypotensive drugs other than the study drugs was prohibited during the study period.

The key inclusion criteria were patients aged ≥20 years with class I or II essential hypertension meeting all of the following:

- The mean of blood pressure measured at the last 2 timepoints in the observation period: ≥140 and <180 mmHg in SBP and ≥90 and <110 mmHg in DBP
- Difference in blood pressure at the last 2 timepoints in the observation period: ≤30 mmHg in SBP and ≤15 mmHg in DBP
- 24-hour blood pressure measured by ambulatory blood pressure monitoring (ABPM) after Week 3 of the observation period: ≥130 mmHg in SBP and ≥80 mmHg in DBP

Subjects were assigned by a stratified randomization using the mean of SBP at the last 2 timepoints in the observation period (<160 mmHg, ≥160 mmHg).

All of the 426 randomized subjects (87 in the placebo group, 83 in the esaxerenone 1.25 mg group, 84 in the esaxerenone 2.5 mg group, 88 in the esaxerenone 5 mg group, 84 in the eplerenone group) received the study drug and were included in the safety analysis population. Of them, 423 subjects (85 subjects, 82 subjects, 84 subjects, 88 subjects, 84 subjects), excluding 3 subjects (2 subjects, 1 subject, 0 subjects, 0 subjects, 0 subjects) without efficacy endpoint data, were included in the full analysis set (FAS) and in the primary efficacy analysis population. Study discontinuation occurred in 23 subjects (10 subjects, 6 subjects, 3 subjects, 2 subjects, 2 subjects), and main reasons for the discontinuation were consent withdrawal in 13 subjects (5 subjects, 2 subjects, 3 subjects, 2 subjects, 1 subjects), adverse events in 4 subjects (2 subjects, 1 subject, 0 subjects, 0 subjects, 1 subject), and meeting the discontinuation criteria in 4 subjects (2 subjects, 2 subjects, 0 subjects, 0 subjects, 0 subjects).

The primary efficacy endpoint was the change from baseline in trough sitting SBP and DBP (mean of the values at the last 2 timepoints in the observation period) to the end of the treatment period (mean of the values at Week 10 and 12 in the treatment period). Tables 26 and 27 show the results in each group. The esaxerenone 2.5 and 5 mg groups showed a significant decrease in both SBP and DBP compared with the placebo group (to adjust for the multiplicity of tests, tests were conducted in the order of "comparison between the esaxerenone 5 mg group and placebo group," "comparison between the esaxerenone 2.5 mg group and placebo group," and "comparison between the esaxerenone 1.25 mg group and placebo group." When both SBP and DBP were found to be significantly different, test on the next dose groups was conducted.).

Table 26. Change in trough sitting SBP (FAS, last observation carried forward [LOCF])

	Placebo (n = 85)	Esaxerenone 1.25 mg (n = 82)	Esaxerenone 2.5 mg (n = 84)	Esaxerenone 5 mg (n = 88)	Eplerenone (n = 84)
Baseline [a] (mmHg)	156.7 ± 9.04	156.4 ± 9.05	156.4 ± 8.43	157.4 ± 9.04	157.9 ± 8.40
At the end of the treatment period[a] (mmHg)	149.8 ± 12.67	145.9 ± 14.31	142.2 ± 12.11	136.7 ± 13.98	140.2 ± 12.45
Change[b,c]	−7.0 [−9.5, −4.6]	−10.7 [−13.2, −8.2]	−14.3 [−16.8, −11.9]	−20.6 [−23.0, −18.2]	−17.4 [−19.9, −15.0]
Difference in change[b,c]	—	−3.6 [−7.1, −0.1] $P = 0.0412$	−7.3 [−10.8, −3.8] $P < 0.0001$	−13.6 [−17.0, −10.1] $P < 0.0001$	—

a: Mean ± SD
b: Least squares mean [two-sided 95% CI]
c: Analysis of covariance (ANCOVA) model with treatment group as the explanatory variable and baseline SBP as the covariate

Table 27. Change in trough sitting DBP (FAS, LOCF)

	Placebo (n = 85)	Esaxerenone 1.25 mg (n = 82)	Esaxerenone 2.5 mg (n = 84)	Esaxerenone 5 mg (n = 88)	Eplerenone (n = 84)
Baseline[a] (mmHg)	96.8 ± 4.95	97.2 ± 5.48	98.6 ± 5.62	97.2 ± 5.43	98.4 ± 5.30
At the end of the treatment period[a] (mmHg)	92.8 ± 8.62	92.2 ± 9.15	91.1 ± 9.21	86.7 ± 9.46	90.0 ± 8.81
Change[b, c]	−3.8 [−5.2, −2.4]	−5.0 [−6.4, −3.6]	−7.6 [−9.1, −6.2]	−10.4 [−11.8, −9.0]	−8.5 [−9.9, −7.1]
Difference in change[b,c]	—	−1.2 [−3.2, 0.8] $P = 0.2389$	−3.8 [−5.9, −1.8] $P = 0.0002$	−6.6 [−8.6, −4.6] $P < 0.0001$	—

a: Mean ± SD
b: Least squares mean [two-sided 95% CI]
c: ANCOVA model with treatment group as the explanatory variable and baseline DBP as the covariate

The safety study showed that the incidence of adverse events was 46.0% (40 of 87) of subjects in the placebo group, 30.1% (25 of 83) of subjects in the esaxerenone 1.25 mg group, 40.5% (34 of 84) of subjects in the esaxerenone 2.5 mg group, 36.4% (32 of 88) of subjects in the esaxerenone 5 mg group, and 36.9% (31 of 84) of subjects in the eplerenone group. Table 28 shows the main adverse events.

Table 28. Main adverse events (safety analysis population)

	Placebo (n = 87)	Esaxerenone 1.25 mg (n = 83)	Esaxerenone 2.5 mg (n = 84)	Esaxerenone 5 mg (n = 88)	Eplerenone (n = 84)
Nasopharyngitis	8.0 (7)	4.8 (4)	7.1 (6)	6.8 (6)	8.3 (7)
Headache	2.3 (2)	1.2 (1)	7.1 (6)	0 (0)	2.4 (2)
Pharyngitis	2.3 (2)	3.6 (3)	6.0 (5)	1.1 (1)	2.4 (2)
Upper respiratory tract inflammation	4.6 (4)	3.6 (3)	4.8 (4)	5.7 (5)	2.4 (2)
Blood potassium increased	2.3 (2)	0 (0)	3.6 (3)	3.4 (3)	1.2 (1)
Musculoskeletal stiffness	0 (0)	0 (0)	3.6 (3)	0 (0)	0 (0)
Blood TG increased	0 (0)	2.4 (2)	2.4 (2)	0 (0)	3.6 (3)
Blood uric acid increased	1.1 (1)	2.4 (2)	1.2 (1)	3.4 (3)	1.2 (1)
Back pain	3.4 (3)	1.2 (1)	1.2 (1)	1.1 (1)	0 (0)
Blood CK increased	3.4 (3)	0 (0)	1.2 (1)	0 (0)	0 (0)
Glomerular filtration rate decreased	1.1 (1)	3.6 (3)	0 (0)	3.4 (3)	0 (0)

% (number of subjects)

No death occurred. Serious adverse events were observed in 2 subjects in the placebo group (bladder cancer, suppurative osteomyelitis) and in 1 subject in the esaxerenone 1.25 mg group (hypertensive emergency), but the causal relationship to the study drug was ruled out.

Adverse events leading to discontinuation of the study drug were observed in 2 subjects in the placebo group (bladder cancer, suppurative osteomyelitis), in 1 subject in the esaxerenone 1.25 mg group (hypertensive emergency), and in 1 subject in the eplerenone group (diarrhoea).

7.3 Phase III study

7.3.1 Phase III study in patients with essential hypertension (Study CS3150-A-J301, CTD 5.3.5.1-2; Study period, September 2016 to July 2017)

A randomized, double-blind, parallel-group study was conducted to compare the efficacy and safety between esaxerenone 2.5 or 5 mg and eplerenone 50 mg in patients with essential hypertension (target sample size, 930 subjects in total [310 per group]) in 44 study sites in Japan.

The placebo was administered during the 4-week observation period. During the subsequent 12-week treatment period, esaxerenone 2.5, or 5 mg or eplerenone 50 mg was administered orally once daily. Administration of hypotensive drugs other than the study drugs was prohibited during the study period.

The key inclusion criteria were patients aged ≥20 years with class I or II essential hypertension who meet all of the following:

- The mean of blood pressure measured at the last 2 timepoints in the observation period: ≥140 and <180 mmHg in SBP and ≥90 and <110 mmHg in DBP
- Difference in blood pressure at the last 2 timepoints in the observation period: ≤30 mmHg in SBP and ≤15 mmHg in DBP

- 24-hour blood pressure measured by ABPM after Week 3 of the observation period: ≥130 mmHg in SBP and ≥80 mmHg in DBP

Subjects were assigned by a stratified randomization using the mean of SBP at the last 2 timepoints in the observation period (<160 mmHg, ≥160 mmHg).

All of the 1001 randomized subjects (331 in the esaxerenone 2.5 mg group, 338 in the esaxerenone 5 mg group, 332 in the eplerenone group) received the study drug and were included in the safety analysis population. Of them, 998 subjects (330 subjects, 337 subjects, 331 subjects), excluding 3 subjects (1 subject, 1 subject, 1 subject) without efficacy endpoint data, were included in FAS. Of them, 944 subjects (306 subjects, 322 subjects, 316 subjects), excluding 53 subjects (24 subjects, 15 subjects, 14 subjects) without primary efficacy endpoint data, 7 subjects (4 subjects, 2 subjects, 1 subject) with violation for prohibited concomitant drugs, 1 subject (0 subjects, 0 subjects, 1 subject) with inclusion/exclusion criteria violation, 1 subject (1 subject, 0 subjects, 0 subjects) with error in study drug allocation, and 1 subject (0 subjects, 0 subjects, 1 subject) for other reason, were included in the per protocol set (PPS) and subjected to the primary efficacy analysis. Study discontinuation occurred in 49 subjects (21 subjects, 15 subjects, 13 subjects). Main reasons for the discontinuation were consent withdrawal in 26 subjects (11 subjects, 8 subjects, 7 subjects), meeting the discontinuation criteria in 10 subjects (5 subjects, 3 subjects, 2 subjects), and adverse events in 9 subjects (5 subjects, 1 subject, 3 subjects).

The primary efficacy endpoint was the change from baseline in trough sitting SBP and DBP (mean of the values at the last 2 timepoints in the observation period) to the end of the treatment period (mean of the values at Week 10 and 12). Tables 29 and 30 show the results in each group. The upper limit of the two-sided 95% CI of the difference in SBP and DBP between the esaxerenone 2.5 mg group and eplerenone group was both below the non-inferiority margin (3.4 mmHg for SBP, 1.5 mmHg for DBP[1)]), demonstrating the non-inferiority of the esaxerenone 2.5 mg group to the eplerenone group.

Table 29. Change in trough sitting SBP (PPS)

	Esaxerenone 2.5 mg (n = 306)	Esaxerenone 5 mg (n = 322)	Eplerenone (n = 316)
Baseline[a] (mmHg)	154.7 ± 9.52	155.3 ± 9.42	155.0 ± 9.59
At the end of the treatment period[a] (mmHg)	141.1 ± 12.48	138.3 ± 12.96	142.8 ± 13.11
Change[b,c]	−13.7 [−14.9, −12.5]	−16.9 [−18.1, −15.7]	−12.1 [−13.3, −10.9]
Difference in change from the eplerenone group[b,c]	−1.6 [−3.3, 0.1]	—	—

a: Mean ± SD
b: Least squares mean [two-sided 95% CI]
c: ANCOVA model with treatment group as the explanatory variable and baseline SBP as the covariate

1) By assuming the difference in the change from baseline in SBP and DBP to Week 12 between the eplerenone 50 mg group and placebo group to be −6.7 mmHg and −2.9 mmHg, respectively, based on the data of past clinical studies on eplerenone, the absolute value of half the difference, i.e., 3.4 mmHg and 1.5 mmHg, respectively, was used as the noninferiority margin.

Table 30. Change in trough sitting DBP (PPS)

	Esaxerenone 2.5 mg (n = 306)	Esaxerenone 5 mg (n = 322)	Eplerenone (n = 316)
Baseline[a] (mmHg)	97.9 ± 5.70	97.7 ± 5.38	98.3 ± 5.54
At the end of the treatment period[a] (mmHg)	91.0 ± 8.40	89.3 ± 8.49	92.1 ± 8.34
Change[b,c]	−6.8 [−7.6, −6.1]	−8.4 [−9.1, −7.7]	−6.1 [−6.8, −5.4]
Difference in change from the eplerenone group[b,c]	−0.7 [−1.8, 0.3]	—	—

a: Mean ± SD
b: Least squares mean [two-sided 95% CI]
c: ANCOVA model with treatment group as the explanatory variable and baseline DBP as the covariate

The safety study showed that the incidence of adverse events was 38.4% (127 of 331) of subjects in the esaxerenone 2.5 mg group, 44.1% (149 of 338) of subjects in the esaxerenone 5 mg group, and 37.0% (123 of 332) of subjects in the eplerenone group. Table 31 shows the main adverse events.

Table 31. Main adverse events (safety analysis population)

	Esaxerenone 2.5 mg (n = 331)	Esaxerenone 5 mg (n = 338)	Eplerenone (n = 332)
Viral upper respiratory tract infection	13.0 (43)	12.1 (41)	14.5 (48)
Upper respiratory tract inflammation	3.6 (12)	3.3 (11)	3.0 (10)
Influenza	3.9 (13)	3.0 (10)	2.4 (8)

% (number of subjects)

No death occurred. Serious adverse events were observed in 4 subjects in the esaxerenone 2.5 mg group (cardiac failure chronic, intervertebral disc protrusion, head injury, subdural haematoma/cerebral haemorrhage), 3 subjects in the esaxerenone 5 mg group (large intestine polyp, breast cancer, leiomyosarcoma), and 1 subject in the eplerenone group (myocardial infarction). A causal relationship to the study drug could not be ruled out for cardiac failure chronic in the esaxerenone 2.5 mg group.

Adverse events leading to discontinuation of the study drug were observed in 5 subjects in the esaxerenone 2.5 mg group (cardiac failure chronic, intervertebral disc protrusion, electrocardiogram T wave inversion, rash generalized, cerebral haemorrhage, altered state of consciousness), 1 subject in the esaxerenone 5 mg group (blood potassium increased), and 3 subjects in the eplerenone group (myocardial infarction, liver function test abnormal, loss of consciousness).

7.3.2 Long-term treatment study in patients with essential hypertension (Study CS3150-A-J302, CTD 5.3.5.2-1; Study period, March 2016 to July 2017)

An open-label study was conducted to investigate the efficacy and safety of a long-term treatment of esaxerenone 2.5 or 5 mg in patients with essential hypertension (target sample size, 360 subjects in total) in 20 study sites in Japan.

The placebo was administered during the 4-week observation period and, during the subsequent Treatment Period I of 12 weeks (Week 0 through 12), esaxerenone was administered orally once daily. The starting dose was 2.5 mg, and the dose was allowed to be increased to 5 mg at Week 4, 6, or 8 at the discretion of the investigator or subinvestigator if SBP was ≥140 mmHg or DBP was ≥90 mmHg (or if SBP was ≥130 mmHg or DBP was ≥80 mmHg in patients with concurrent diabetes mellitus) and if

serum potassium level was <5.1 mEq/L (<4.8 mEq/L if the patient received in combination with a renin angiotensin [RA] inhibitor). During the Treatment Period II (from the end of the Treatment Period I through Week 28 or 52), administration of esaxerenone was continued at the same dose as given at the end of the Treatment Period I. During the Treatment Period II, dose adjustment of esaxerenone or concomitant drugs was allowed at the discretion of the investigator or subinvestigator in case of insufficient or excessive blood pressure decrease. As for the dose increase, the dose of esaxerenone was increased in preference to concomitant drugs. If the patient had already been receiving 5 mg of esaxerenone, the dose of concomitant hypotensive drug was increased or a new hypotensive drug was added. As for the dose reduction, if other hypotensive drugs were being concomitantly administered, the dose of these concomitant hypotensive drugs were reduced or discontinued in preference to esaxerenone, and only when necessitated, the dose of esaxerenone was to be reduced or discontinued.

Subjects who had been receiving hypotensive drugs from ≥4 weeks before the observation period were allowed to receive either one of the calcium channel blocker (CCB) or RA inhibitor after the start of the observation period, without changing the dosage regimen from the start of the observation period up to the end of Treatment Period I.

The key inclusion criteria were patients aged ≥20 years with essential hypertension meeting all of the following:

- The mean of blood pressure measured at the last 2 timepoints in the observation period: ≥140 and <180 mmHg in SBP and ≥90 and <110 mmHg in DBP
- Difference in blood pressure at the last 2 timepoints in the observation period: ≤30 mmHg in SBP and ≤15 mmHg in DBP
- 24-hour blood pressure measured by ABPM after Week 3 of the observation period: ≥130 mmHg in SBP and ≥80 mmHg in DBP

All of the 368 subjects enrolled in the study (245 in the esaxerenone monotherapy group, 64 in the esaxerenone + RA inhibitor group, 59 in the esaxerenone + CCB group) received the study drug and were included in the safety analysis population and FAS. The FAS was handled as the primary analysis population. Study discontinuation occurred in 18 subjects (18 subjects, 0 subjects, 0 subjects). Main reasons for the discontinuation were withdrawal of consent in 9 subjects (9 subjects, 0 subjects, 0 subjects) and adverse events in 3 subjects (3 subjects, 0 subjects, 0 subjects). The dose of esaxerenone was increased to 5 mg in 237 subjects (160 subjects, 37 subjects, 40 subjects) during Treatment Period I, and 264 subjects (183 subjects, 39 subjects, 42 subjects) were receiving 5 mg at the end of the treatment period.

The primary efficacy endpoint was the changes in trough sitting SBP and DBP from the end of the run-in period to the end of the treatment period. Table 32 and 33 show results in each group.

Table 32. Change in trough sitting SBP (mmHg) (FAS, LOCF)

	Esaxerenone monotherapy (n = 245)	Esaxerenone + CCB (n = 59)	Esaxerenone + RA inhibitor (n = 64)
Baseline	155.4 ± 10.02	154.2 ± 9.15	155.2 ± 8.59
At Week 12	139.2 ± 12.13	139.4 ± 12.50	138.4 ± 13.04
Change at Week 12	−16.3 ± 11.88	−14.8 ± 11.30	−16.8 ± 11.78
At Week 28	135.8 ± 11.48	137.6 ± 10.09	136.8 ± 12.05
Change at Week 28	−19.6 ± 12.33	−16.6 ± 11.78	−18.4 ± 11.31
At Week 52	132.0 ± 11.11	133.9 ± 7.05	131.0 ± 10.13
Change at Week 52	−23.7 ± 12.74	−20.5 ± 10.23	−23.0 ± 11.08

Mean ± SD

Table 33. Change in trough sitting DBP (mmHg) (FAS, LOCF)

	Esaxerenone monotherapy (n = 245)	Esaxerenone + CCB (n = 59)	Esaxerenone + RA inhibitor (n = 64)
Baseline	97.5 ± 5.14	97.8 ± 5.11	99.8 ± 5.72
At Week 12	90.4 ± 8.32	89.7 ± 7.79	90.2 ± 8.93
Change at Week 12	−7.0 ± 7.19	−8.2 ± 6.32	−9.6 ± 8.53
At Week 28	87.7 ± 7.86	88.4 ± 7.71	88.8 ± 8.21
Change at Week 28	−9.8 ± 7.16	−9.4 ± 6.42	−11.0 ± 8.05
At Week 52	84.0 ± 7.96	84.1 ± 7.14	86.1 ± 8.76
Change at Week 52	−12.3 ± 7.45	−13.1 ± 6.17	−12.6 ± 6.78

Mean ± SD

The safety study showed that the incidence of adverse events was 65.3% (160 of 245) of subjects in the esaxerenone monotherapy group, 78.0% (46 of 59) of subjects in the esaxerenone + CCB group, and 73.4% (47 of 64) of subjects in the esaxerenone + RA inhibitor group. Table 34 shows the main adverse events.

Table 34. Main adverse events (safety analysis population)

	Esaxerenone monotherapy (n = 245)	Esaxerenone + CCB (n = 59)	Esaxerenone + RA inhibitor (n = 64)
Viral upper respiratory tract infection	22.0 (54)	35.6 (21)	40.6 (26)
Blood potassium increased	7.8 (19)	1.7 (1)	9.4 (6)
Dermatitis contact	4.1 (10)	0 (0)	1.6 (1)
Headache	3.7 (9)	0 (0)	0 (0)
Upper respiratory tract inflammation	3.3 (8)	5.1 (3)	6.3 (4)
Bronchitis	3.3 (8)	0 (0)	0 (0)
Upper respiratory tract infection	3.3 (8)	0 (0)	0 (0)
Gastroenteritis	2.9 (7)	1.7 (1)	3.1 (2)
Diarrhoea	2.9 (7)	1.7 (1)	3.1 (2)
Back pain	2.4 (6)	3.4 (2)	6.3 (4)
Influenza	2.4 (6)	1.7 (1)	6.3 (4)
Renal dysfunction	2.4 (6)	0 (0)	3.1 (2)
Dental caries	2.0 (5)	0 (0)	4.7 (3)
Hepatic function abnormal	1.6 (4)	5.1 (3)	0 (0)
Hyperuricaemia	1.2 (3)	10.2 (6)	0 (0)
Arthralgia	1.2 (3)	8.5 (5)	1.6 (1)
Anaemia	1.2 (3)	5.1 (3)	0 (0)
Insomnia	1.2 (3)	3.4 (2)	0 (0)
Gout	0.8 (2)	3.4 (2)	0 (0)
Pharyngitis	0.8 (2)	0 (0)	3.1 (2)
Abdominal discomfort	0.8 (2)	0 (0)	3.1 (2)
Cough	0.8 (2)	0 (0)	3.1 (2)
Pain in extremity	0.8 (2)	0 (0)	3.1 (2)
Gingivitis	0.4 (1)	5.1 (3)	0 (0)
Dizziness	0.4 (1)	1.7 (1)	3.1 (2)
Eczema	0 (0)	5.1 (3)	1.6 (1)
Prurigo	0 (0)	3.4 (2)	0 (0)
Stomatitis	0 (0)	0 (0)	3.1 (2)
Myalgia	0 (0)	0 (0)	3.1 (2)

% (number of subjects)

No death occurred. Serious adverse events were observed in 3 subjects in the esaxerenone monotherapy group (colon cancer, lumbar spinal stenosis, and large intestine polyp), but their causal relationship to the study drug was ruled out.

Adverse events leading to discontinuation of the study drug were observed in 3 subjects in the esaxerenone monotherapy group (blood potassium increased, dizziness, and angina pectoris).

7.3.3 Phase III study in hypertensive patients with moderate renal impairment (Study CS3150-A-J305, CTD 5.3.5.2-4; Study period, June 2016 to May 2017)

An open-label study was conducted to investigate the efficacy and safety of esaxerenone in concomitant use with an ARB or ACE inhibitor in hypertensive patients with moderate renal impairment (target sample size, 50 subjects in total) in 14 study sites in Japan.

Esaxerenone was administered orally once daily during the 12-week treatment period after a 4-week observation period. The starting dose of esaxerenone was 1.25 mg. The dose was allowed to be increased to 2.5 mg at Week 4, 6, or 8 of the treatment period at the discretion of the investigator or subinvestigator if SBP was ≥130 mmHg or DBP was ≥80 mmHg and serum potassium level was <4.8 mEq/L and if eGFR, over the last 2 weeks after the previous visit, did not decrease by ≥30% from the level at Week 3 of the observation period. The dose was allowed to be increased to 5 mg at Week 8 only in subjects who increased the dose to 2.5 mg at Week 4, according to the criteria as those for the dose increase from 1.25

mg to 2.5 mg. The dose was allowed to be reduced if, during the treatment period, (1) serum potassium level increased to ≥6.0 mEq/L, or (2) serum potassium level was ≥5.5 mEq/L and <6.0 mEq/L and the same results were obtained by the repeated test, or (3) excessive hypotensive symptoms were observed and dose reduction was considered necessary by the investigator or subinvestigator.

Throughout the observation period and the treatment period, either an ARB or ACE inhibitor was administered at a constant dosage regimen.

The key inclusion criteria were patients aged ≥20 and ≤80 years with hypertension meeting all of the following conditions:

- The mean of blood pressure measured at Week 3 of the observation period and at the end of the observation period: ≥140 and <180 mmHg in SBP and ≥80 and <110 mmHg in DBP
- Difference in blood pressure at Week 3 of the observation period and at the end of the observation period: ≤30 mmHg in SBP and ≤15 mmHg in DBP
- eGFR calculated from serum creatinine level during the observation period: ≥30 and <60 mL/min/1.73 m^2

All of the 58 subjects enrolled in the study received the study drug and were included in the safety analysis population and FAS, and the FAS was handled as the primary efficacy analysis population. Study discontinuation occurred in 3 subjects. Reasons for the discontinuation were adverse events in 1 subject, no return visit at Week 12 in 1 subject, and poor blood pressure control in 1 subject. The dose of esaxerenone was increased to 2.5 mg in 54 subjects. The dose was further increased to 5 mg in 25 of 54 subjects, and the administration was continued until the end of the treatment period.

Table 35 shows efficacy results, i.e., the change from baseline in trough sitting SBP and DBP (mean of the values at Week 3 in the observation period and at the end of the observation period) to the end of the treatment period (mean of the values at Week 10 and 12 in the treatment period).

Table 35. Change in trough sitting SBP and DBP (mmHg) (FAS, LOCF)

	SBP	DBP
	N = 58	
Baseline	159.4 ± 10.85	91.8 ± 7.31
At the end of the treatment period	141.5 ± 14.11	83.7 ± 9.19
Change at the end of the treatment period	−17.8 ± 11.89	−8.1 ± 6.25

Mean ± SD

The safety study showed that the incidence of adverse events was 60.3% (35 of 58) of subjects. Main adverse events were viral upper respiratory tract infection in 12.1% (7 of 58) of subjects, blood potassium increased in 10.3% (6 of 58) of subjects, blood creatinine increased in 5.2% (3 of 58) of subjects, blood uric acid increased in 5.2% (3 of 58) of subjects, and the glomerular filtration rate decreased in 5.2% (3 of 58) of subjects.

There were neither deaths nor serious adverse events.

An adverse event leading to discontinuation of the study drug was observed in 1 subject (hepatic function abnormal).

7.3.4 Phase III study in hypertensive patients with type 2 diabetes mellitus and albuminuria (Study CS3150-A-J306, CTD 5.3.5.2-6; Study period, July 2016 to March 2017)

An open-label study was conducted to investigate the efficacy and safety of esaxerenone in hypertensive patients with type 2 diabetes mellitus and albuminuria (target sample size, 50 subjects in total) in 13 study sites in Japan.

Esaxerenone was administered orally once daily during the 12-week treatment period after a 4-week observation period. The starting dose of esaxerenone was 1.25 mg. The dose was allowed to be increased to 2.5 mg at Week 4, 6, or 8 of the treatment period at the discretion of the investigator or subinvestigator if SBP was ≥130 mmHg or DBP was ≥80 mmHg and serum potassium level was <4.8 mEq/L and if eGFR, over the last 2 weeks after the previous visit, did not decrease by ≥30% from the level at Week 3 of the observation period. The dose was allowed to be increased to 5 mg at Week 8 only in subjects who increased the dose to 2.5 mg at Week 4, according to the criteria as those for the dose increase from 1.25 mg to 2.5 mg. The dose was allowed to be reduced if, during the treatment period, (1) serum potassium level increased to ≥6.0 mEq/L, or (2) serum potassium level was ≥5.5 mEq/L and <6.0 mEq/L and the same results were obtained by the repeated test, or (3) excessive hypotensive symptoms were observed and dose reduction was considered necessary by the investigator or subinvestigator.

Throughout the observation period and the treatment period, either an ARB or ACE inhibitor was administered at a constant dosage regimen.

The key inclusion criteria were patients aged ≥20 and ≤80 years with hypertension meeting all of the following conditions:

- Patients with type 2 diabetes mellitus who meet all of the following:
  - ✓ Urine albumin-to-creatinine ratio (UACR) in the first morning urine measured 3 times during the observation period: ≥30 mg/g Cr and <1000 mg/g Cr twice or more
  - ✓ eGFR during the observation period: ≥30 mL/min/1.73 m^2
- The mean of blood pressure measured at Week 3 of the observation period and at the end of the observation period: ≥140 and <180 mmHg in SBP and ≥80 and <110 mmHg in DBP
- Difference in blood pressure at Week 3 of the observation period and at the end of the observation period: ≤30 mmHg in SBP and ≤15 mmHg in DBP

All of the 51 subjects enrolled in the study received the study drug and were included in the safety analysis population and FAS, and the FAS was handled as the primary efficacy analysis population. Study discontinuation occurred in 4 subjects. The reasons for the discontinuation were adverse events in 2 subjects, withdrawal of consent in 1 subject, and physician's judgment in 1 subject. The dose of esaxerenone was increased to 2.5 mg in 44 subjects, then to 5 mg in 19 of 44 subjects, and the administration was continued at the same dose except in 1 subject whose dose was reduced to 1.25 mg from 2.5 mg.

Table 36 shows the efficacy results, i.e., the change from baseline in trough sitting SBP and DBP (mean of the values at Week 3 of the observation period and the value at the end of the observation period) to the end of the treatment period (mean of Week 10 and 12).

Table 36. Change in trough sitting SBP and DBP (mmHg) (FAS, LOCF)

	SBP	DBP
	N = 51	
Baseline	158.7 ± 10.94	89.0 ± 5.88
At the end of the treatment period	145.0 ± 17.52	82.8 ± 7.76
Change at the end of the treatment period	−13.7 ± 13.92	−6.2 ± 5.68

Mean ± SD

The safety study showed that the incidence of adverse events was 49.0% (25 of 51) of subjects. Main adverse events were viral upper respiratory tract infection in 19.6% (10 of 51) of subjects, blood potassium increased in 11.8% (6 of 51) of subjects, and back pain in 3.9% (2 of 51) of subjects.

No death occurred. A serious adverse event was observed in 1 subject (thrombotic cerebral infarction), and its causal relationship to the study drug could not be ruled out.

Adverse events leading to discontinuation of the study drug were observed in 2 subjects (thrombotic cerebral infarction and rash generalized).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning and indication

The applicant's explanation about the clinical positioning of esaxerenone in the drug therapy of hypertension:

Esaxerenone is an MR antagonist which lowers blood pressure by selectively binding to MR, thereby inhibiting aldosterone-induced MR activation. According to The Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2014 (The Japanese Society of Hypertension, 2014), MR antagonists are considered to be useful for low renin hypertension, refractory hypertension, hypertension with cardiac disease, etc. They are expected to be effective in lowering blood pressure in hypertensive conditions associated with aldosterone or MR, and there are certain needs for such hypertension treatment. In Japan, spironolactone and eplerenone are approved as MR antagonists. Although spironolactone has a antihypertensive effect due to its potent MR inhibitory activity, sex hormone-mediated adverse drug reactions are reported because of its low MR specificity (*Hypertens Res*. 2013;36(3):185-90, *J Hypertens*. 2013;31(1):3-15). Eplerenone is a hypotensive drug highly selective for MR with attenuated adverse drug reactions associated with sex hormone receptors. However, it is contraindicated in hypertensive patients with moderate or severe renal impairment and in diabetic patients with microalbuminuria or proteinuria. Clinical studies have demonstrated that esaxerenone is similarly effective in lowering blood pressure as eplerenone almost without sex hormone-related events. Also, the clinical study on hypertensive patients with moderate renal impairment or type 2 diabetes mellitus and albuminuria showed that, in these patients, esaxerenone could be administered safely by suppressing increase in serum potassium level by gradually increasing the dose from 1.25 mg while checking serum potassium level. Based on the above, the applicant considers that esaxerenone has

overcome the drawbacks of conventional MR antagonists and thus provides a new treatment option for patients with hypertension, even those in whom conventional MR antagonists are contraindicated.

PMDA's view:
In The Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2014 (The Japanese Society of Hypertension, 2014), MR antagonists are not positioned as the first-line drugs for the treatment of hypertension, but they are expected to be particularly effective for low renin hypertension and are useful also for refractory hypertension. Esaxerenone has been demonstrated to be non-inferior to the MR antagonist eplerenone in clinical studies in patients with essential hypertension [see Section "7.R.2 Efficacy and dosage regimen"]. Esaxerenone is highly selective for MR compared with drugs in the same class [see Section "3.R.1 Effect on hypertension"], without sex hormone-related adverse events as reported for spironolactone or any other significant safety problems [see Section "7.R.3 Safety"]. Therefore, esaxerenone is a treatment option for hypertension, as is the case with the conventional MR antagonist eplerenone. PMDA concludes that the proposed indication of "hypertension" is appropriate from the submitted clinical study data.

In clinical studies on esaxerenone, the percentage of subjects showing serum potassium level of ≥5.5 mEq/L tended to be higher in the esaxerenone group than in the eplerenone group. However, taking account of clinical study results (in which esaxerenone was administered at a low starting dose of 1.25 mg) on patients for whom eplerenone is contraindicated in hypertension treatment, i.e., patients with moderate renal impairment and diabetic patients with microalbuminuria or proteinuria, esaxerenone may be administered to these patients, provided that precautions are given for possible increase in serum potassium level, that patients to be treated are selected carefully, and that serum potassium level is measured frequently enough [see Section "7.R.2.3 Administration to patients with moderate renal impairment" and Section "7.R.2.4 Administration to patients with diabetes mellitus with albuminuria or proteinuria"].

7.R.2 Efficacy and dosage and administration

7.R.2.1 Starting dose and maximum dose

The applicant's explanation about the starting dose and the maximum dose of esaxerenone:
In the dose-finding study (Study J203), the change from baseline in SBP and DBP to the end of the treatment period was significantly greater in the esaxerenone 2.5 and 5 mg groups than in the placebo group. In the reference groups (eplerenone 50-100 mg), the extent of the change from baseline in SBP and DBP was between that in the esaxerenone 2.5 mg and that in the esaxerenone 5 mg group. As for safety, the incidence of adverse events did not show a marked difference between the treatment groups, and the observed adverse events were mild or moderate in severity. Serum potassium level of ≥5.5 mEq/L was observed in 1.1% (1 of 87) of subjects in the placebo group, 0% (0 of 83) of subjects in the esaxerenone 1.25 mg group, 3.6% (3 of 84) of subjects in the esaxerenone 2.5 mg group, 2.3% (2 of 88) of subjects in the esaxerenone 5 mg group, and 0% (0 of 84) of subjects in the eplerenone group.

Based on the above results, a confirmatory study (Study J301) was conducted in patients with essential hypertension (1) to compare the safety and demonstrate the non-inferiority in the antihypertensive effect of once daily administration of esaxerenone (2.5 mg), the estimated standard dose, compared with once

daily administration of eplerenone at the standard dose (50 mg) and (2) to compare the antihypertensive effect between esaxerenone 2.5 mg and 5 mg. The upper limit of two-sided 95% CI of the between-group difference in the change from baseline in SBP and DBP to the end of the treatment period was below the prescribed non-inferiority margin, demonstrating the non-inferiority of esaxerenone 2.5 mg to eplerenone 50 mg. The study also showed a greater antihypertensive effect in the esaxerenone 5 mg group than in the esaxerenone 2.5 mg group. As for safety, no marked difference was observed in the incidence of adverse events between the treatment groups, and the observed adverse events were mild to moderate in severity. Serum potassium level was ≥5.5 mEq/L in 4.5% (15 of 331) of subjects in the esaxerenone 2.5 mg group, 3.0% (10 of 338) of subjects in the esaxerenone 5 mg group, and 1.8% (6 of 332) of subjects in the eplerenone 50 mg group.

In the long-term treatment study (Study J302), the starting dose of esaxerenone was 2.5 mg, and the dose was allowed to be increased to 5 mg if blood pressure is not adequately controlled. As a result, 71.7% (264 of 368) of subjects ended up receiving 5 mg of esaxerenone, and blood pressure decreased from the level before the dose increase in these subjects. No safety problems were observed during the long-term treatment period with or without dose increase.

Based on the above results, the applicant considers that it is appropriate that both the starting dose and the standard dose of esaxerenone be 2.5 mg, the dose which is similarly effective in lowering blood pressure as eplerenone 50 mg, the starting dose and the standard dose in treating hypertension. Also, it is appropriate that the maximum dose is 5 mg, the dose that has been shown to be safe and is expected to be superior to 2.5 mg in the antihypertensive effect.

PMDA's view:
The submitted clinical study data have demonstrated the antihypertensive effect of esaxerenone 2.5 mg. It is therefore acceptable that esaxerenone 2.5 mg would be the starting dose and the standard dose, because esaxerenone 2.5 mg is shown to be non-inferior in lowering blood pressure to eplerenone 50 mg, the starting dose and the standard dose of eplerenone in treating hypertension. Also, Studies J203 and J301 have demonstrated that esaxerenone 5 mg is more effective in lowering blood pressure than esaxerenone 2.5 mg, and that there were no adverse events unique to the esaxerenone 5 mg group or those that showed marked increase in the incidence or severity in the 5 mg group. In addition, taking account of the fact that, in Study J302, esaxerenone 5 mg was still administered to 71.7% of the entire subjects at Week 52 of administration, demonstrating that esaxerenone had been administered at this dose over a long-period of time, it is acceptable to select the maximum dose at 5 mg. However, since the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was higher in the esaxerenone group than in the eplerenone group both in Studies J203 and J301, it is necessary to give appropriate precaution against increase in serum potassium level and to specify the frequency of measuring serum potassium level to ensure the safety of patients. The frequency of the measurement will be discussed in detail in the Safety section.

7.R.2.2 Low dose (1.25 mg) administration

The applicant's explanation about the appropriateness of including the low dose (1.25 mg) of esaxerenone as a treatment option:

Studies J305 and J306 were conducted in hypertensive patients with moderate renal impairment and hypertensive patients with type 2 diabetes mellitus and albuminuria, and these patients have a risk of developing increased serum potassium level and decreased eGFR. To mitigate the risk, esaxerenone was administered at the starting dose of 1.25 mg (half the standard dose), and the dose was increased carefully while evaluating serum potassium level, blood pressure, etc. As a result, a favorable antihypertensive effect was achieved in each of the studies without any significant safety problems. The dose of esaxerenone was not increased from 1.25 mg in 11 subjects (4 subjects in Study J305, 7 subjects in Study J306), the 12-week treatment was completed without dose increase in 9 subjects (4 subjects, 5 subjects), and administration was discontinued at 1.25 mg in 2 subjects (0 subjects, 2 subjects). In 9 subjects who completed 12-week treatment period without dose increase from 1.25 mg, the changes in SBP and DBP were −34 to 0 mmHg and −22 to 0 mmHg, respectively, with an antihypertensive effect being observed in 7 subjects (4 subjects, 3 subjects). Serum potassium level increased to ≥5.5 mEq/L in 3 subjects (2 subjects, 1 subject), while there were no subjects who met the discontinuation criteria, i.e., serum potassium level ≥6.0 mEq/L once or ≥5.5 mEq/L twice in consecutive measurements. Also, there were no subjects in whom blood pressure or renal function decreased substantially from baseline. From these results, it is expected that esaxerenone 1.25 mg is effective in lowering blood pressure in patients with moderate renal impairment and diabetic patients with albuminuria or proteinuria, and that the benefit of continued administration of 1.25 mg outweighs the risk. However, DBP did not show a significantly greater decrease in the esaxerenone 1.25 mg group than the placebo group in Study J203. Therefore, if the dose of esaxerenone cannot be increased from 1.25 mg due to an increase in serum potassium level, the physician should consider discontinuing esaxerenone and switching to other hypotensive drug(s) while checking the conditions of the patient, instead of unnecessarily continuing the treatment at 1.25 mg.

PMDA's view:

In Studies J305 and J306, only 9 subjects completed the 12-week administration without dose increase from 1.25 mg, precluding rigorous evaluation of the efficacy of esaxerenone 1.25 mg in this patient group. Eplerenone is contraindicated in hypertensive patients with moderate renal impairment and hypertensive patients with diabetes mellitus and microalbuminuria or proteinuria because of the concern about hyperkalaemia. Esaxerenone also may increase hyperkalaemia in these patients. In fact, serum potassium level increased to ≥5.5 mEq/L in 3 subjects receiving esaxerenone 1.25 mg. On the other hand, when esaxerenone was administered at the starting dose of 1.25 mg and the dose was increased while frequently checking serum potassium level under careful monitoring of the subjects, there were no subjects who showed serum potassium level of ≥6.0 mEq/L once or ≥5.5 mEq/L twice in consecutive measurements, while the treatment showed a certain antihypertensive effect. These results suggest that it is of clinical significance to provide a treatment option of esaxerenone 1.25 mg to the patient population who may experience hyperkalaemia. The dosage and administration for patients with moderate renal impairment and diabetic patients with albuminuria or proteinuria as well as the appropriate precautionary statement will be discussed in detail in the next and subsequent sections.

7.R.2.3 Administration to patients with moderate renal impairment

The applicant's explanation about administration of esaxerenone to patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2):

In Study J305 in hypertensive patients with moderate renal impairment, esaxerenone was administered at the starting dose of 1.25 mg in combination with an ACE inhibitor or an ARB, and the dose of esaxerenone was allowed to be increased up to the maximum dose of 5 mg depending on blood pressure, serum potassium level, eGFR, etc. [see Section "7.3.3 Phase III study in patients with hypertension with moderate renal impairment"]. As for efficacy, the study showed changes from baseline in sitting blood pressure to the end of the treatment, as shown in Table 35, demonstrating a favorable antihypertensive effect. As for safety, the incidence of adverse events was 60.3% (35 of 58) of subjects, and main adverse events were viral upper respiratory tract infection in 12.1% (7 of 58) of subjects, blood potassium increased in 10.3% (6 of 58) of subjects, blood creatinine increased in 5.2% (3 of 58) of subjects, blood uric acid increased in 5.2% (3 of 58) of subjects, and the glomerular filtration rate decreased in 5.2% (3 of 58) of subjects. There were no severe adverse events. Adverse events rated as moderate were head discomfort, back pain, rib fracture, and wrist fracture in 1 subject each. All other adverse events were rated as mild. Serum potassium level of ≥5.5 mEq/L was observed in 12.1% (7 of 58) of subjects, and the dose of esaxerenone at the occurrence of the increased serum potassium level was 1.25 mg in 2 subjects and 2.5 mg in 5 subjects. The basal concomitant hypotensive agent was ARB in 6 subjects and ACE inhibitor in 1 subject. In all subjects who showed a serum potassium level of ≥5.5 mEq/L in this study, the increase was transient. There were no subjects who met the criteria for dose reduction or discontinuation, i.e., serum potassium level ≥6.0 mEq/L once or ≥5.5 mEq/L twice in consecutive measurements, and administration of esaxerenone was continued without dose reduction or discontinuation. The above results suggest (1) that it is possible to decrease the risk of hyperkalaemia in patients with moderate renal impairment provided that the treatment is started at 1.25 mg and the dose is adjusted or discontinued appropriately depending on the serum potassium level measured frequently, and (2) that such a treatment method is effective in lowering blood pressure. The applicant therefore considers that it is appropriate to include patients with moderate renal impairment as those eligible for the treatment with esaxerenone.

PMDA's view:

It is considered that patients with moderate renal impairment have a particularly high risk of developing hyperkalaemia under administration of an MR antagonist, and eplerenone, the drug in the same class, is contraindicated for treatment of hypertension in this patient group. Since study J305 was an open-label, uncontrolled study and only 58 patients with moderate renal impairment were enrolled, obtained data should be evaluated with caution. Nevertheless, the sitting blood pressure decreased from baseline, suggesting that esaxerenone has a certain level of efficacy. However, in Study J305 as well, serum potassium level increased to ≥5.5 mEq/L in 12.1% (7/58) of subjects receiving esaxerenone, which was even higher than subjects in the esaxerenone group of Study J301 which excluded patients with eGFR of <60 mL/min/1.73 m^2, and the increased serum potassium level was observed in 2 subjects who started the treatment at 1.25 mg, i.e., half the standard starting dose. Thus, the possibility cannot be excluded that hyperkalaemia would occur frequently in patients with moderate renal impairment even if the administration of esaxerenone is started at 1.25 mg, warranting careful attention. In Study J305, the administration of esaxerenone was started at 1.25 mg, and serum potassium level was measured

frequently. As a result, there were no subjects who showed serum potassium level of ≥6.0 mEq/L once or ≥5.5 mEq/L twice in consecutive measurements, and the dose of esaxerenone could be increased to 2.5 mg in 93.1% (54 of 58) of subjects and to 5 mg in 43.1% (25 of 58) of subjects despite concomitant use with ACE inhibitor or ARB, drugs that possibly enhance increase in serum potassium level, and administration of esaxerenone could be continued without dose reduction. From these results, PMDA concludes that it is possible to administer esaxerenone to patients with moderate renal impairment provided that the treatment is carefully performed at the starting dose of 1.25 mg and the dose is increased carefully from 4 weeks after the start of the administration while serum potassium level is measured frequently. The appropriateness of treating this patient group with esaxerenone, dosage and administration, dose adjustment, and the frequency of serum potassium level measurement will be finalized, also taking account of the comments raised in the Expert Discussion.

7.R.2.4 Administration to diabetic patients with albuminuria or proteinuria

The applicant's explanation about the efficacy and safety of esaxerenone in diabetic patients with albuminuria or proteinuria:

In Study J306, esaxerenone was administered to hypertensive patients with type 2 diabetes mellitus and albuminuria in combination with an ACE inhibitor or an ARB, at the same dosage and administration as in Study J305. The efficacy study showed changes from baseline in sitting blood pressure to the end of the treatment, as shown in Table 36, demonstrating a favorable antihypertensive effect. As for safety, the incidence of adverse events was 49.0% (25 of 51) of subjects, and main adverse events (events reported by ≥2 subjects) were viral upper respiratory tract infection in 19.6% (10 of 51) of subjects, blood potassium increased in 11.8% (6 of 51) of subjects, and back pain in 3.9% (2 of 51) of subjects. There were no severe adverse events. Moderate adverse events occurred in 2 subjects (thrombotic cerebral infarction, rash generalized). All other adverse events were mild. Serum potassium level increased to ≥5.5 mEq/L in 3.9% (2 of 51) of subjects: in 1, the level was ≥5.5 mEq/L twice in consecutive measurements but decreased to the reference level at the end of the treatment period after esaxerenone was reduced from 2.5 mg to 1.25 mg. The above results suggest that it is possible to reduce the risk of hyperkalaemia in diabetic patients with albuminuria or proteinuria by specifying esaxerenone is administered at the starting dose of 1.25 mg, serum potassium level is measured frequently, and the dose is adjusted or discontinued appropriately according to the level observed. And such a treatment method is effective in lowering blood pressure. Therefore, the applicant considers it appropriate to treat hypertensive patients with diabetes mellitus and albuminuria or proteinuria with esaxerenone.

PMDA's view:

It is considered that diabetic patients with albuminuria or proteinuria have a particularly high risk of developing hyperkalaemia under administration of an MR antagonist, and eplerenone, the drug in the same class, is contraindicated for treatment of hypertension in this patient group. Study J306 was an open-label, uncontrolled study, and only 51 diabetic patients with albuminuria were enrolled, warranting careful evaluation of the study results obtained. Nevertheless, the sitting blood pressure decreased from baseline, suggesting that esaxerenone has a certain level of efficacy. However, in Study J306 as well, there were subjects who showed serum potassium level of ≥5.5 mEq/L under administration of esaxerenone, raising the possibility that esaxerenone, even at the starting dose of 1.25 mg, causes hyperkalaemia frequently in this patient group, warranting sufficient caution. In Study J306, in which

esaxerenone was administered at the starting dose of 1.25 mg and serum potassium level was measured frequently, there were no subjects who showed serum potassium level of ≥6.0 mEq/L, and the dose of esaxerenone was increased to 2.5 mg in 86.3% (44 of 51) of subjects and to 5 mg in 37.3% (19 of 51) of subjects. One subject showed serum potassium level of ≥5.5 mEq/L in 2 consecutive measurements, but treatment with esaxerenone could be continued at a reduced dose and favorable antihypertensiveeffect was obtained. From these results, PMDA concludes that it is possible to administer esaxerenone to diabetic patients with albuminuria or proteinuria provided that the treatment is given at the starting dose of 1.25 mg and the dose is increased carefully from 4 weeks after the start of the administration while serum potassium level is measured frequently. The appropriateness of treating this patient group with esaxerenone, dosage and administration, dose adjustment, and the frequency of serum potassium level measurement will be finalized, also taking account of the comments raised in the Expert Discussion.

7.R.3 Safety

7.R.3.1 Hyperkalaemia

The applicant's explanation about hyperkalaemia associated with esaxerenone:

Table 37 shows the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L. In Studies J203 and J301, the percentage of subjects showing serum potassium level of ≥5.5 mEq/L was greater in the esaxerenone group than in the eplerenone group, but the increase was transient in most of them and returned to <5.5 mEq/L within several days without any intervening treatment while the administration was continued at the same dose. In Study J301, 5 subjects (3 in the esaxerenone 2.5 mg group, 2 in the esaxerenone 5 mg group) met the discontinuation criteria (serum potassium level of ≥6.0 mEq/L once or ≥5.5 mEq/L in 2 consecutive measurements) but the level returned to <5.5 mEq/L after discontinuation of the study drug in all of them.

Table 37. Percentage of subjects who showed serum potassium level of ≥5.5 mEq/L in each clinical study (safety analysis population)

J203					J301			J302
Placebo (n = 87)	Esaxerenone 1.25 mg (n = 83)	Esaxerenone 2.5 mg (n = 84)	Esaxerenone 5 mg (n = 88)	Eplerenone (n = 84)	Esaxerenone 2.5 mg (n = 331)	Esaxerenone 5 mg (n = 338)	Eplerenone (n = 332)	Esaxerenone (n = 368)
1.1 (1)	0 (0)	3.6 (3)	2.3 (2)	0 (0)	4.5 (15)	3.0 (10)	1.8 (6)	5.4 (20)

% (number of subjects)

In order to identify factors prone to develop hyperkalaemia, a subpopulation analysis was performed on the data of Studies J301 and J302. Results showed that subjects with serum potassium level of ≥4.5 mEq/L during the observation period tended to be predominant among those who showed serum potassium level of ≥5.5 mEq/L. Taking account of the mechanism of action of esaxerenone and of the precautionary statement for the drug in the same class, the applicant considers that, the upper limit of serum potassium level, which is considered to be clinically significant, should be 5.0 mEq/L, and in the package insert, esaxerenone should be contraindicated in patients with hyperkalaemia and for those with serum potassium level exceeding 5.0 mEq/L at the start of administration of esaxerenone.

Regarding the description "the dose should not be increased if serum potassium level has exceeded 5.0 mEq/L," in the "Precautions for Dosage and Administration" section of the package insert (draft),

PMDA asked the applicant to explain whether dose reduction is necessary if the level has exceeded 5.0 mEq/L.

The applicant's explanation:
Among subjects who showed serum potassium level of ≥5.1 mEq/L and <5.5 mEq/L in Studies J203, J301, and J302, the percentage of subjects in whom serum potassium level increased subsequently to ≥5.5 mEq/L was 14.3% (2 of 14) of subjects, 8.7% (9 of 104) of subjects, and 11.3% (7 of 62) of subjects, respectively, and the percentage of subjects who met the discontinuation criterion regarding serum potassium level (≥6.0 mEq/L once or ≥5.5 mEq/L twice in consecutive measurements) was 0% (0 of 14) of subjects, 1.9% (2 of 104) of subjects, and 1.6% (1 of 62) of subjects. Among subjects who showed serum potassium level of ≥5.1 mEq/L and <5.5 mEq/L in Study J305 or J306 in patients with moderate renal impairment or patients with type 2 diabetes mellitus with albuminuria, the percentage of subjects who subsequently showed serum potassium level of ≥5.5 mEq/L was 16.7% (3 of 18) of subjects and 7.7% (1 of 13) of subjects, respectively, and the percentage of subjects who met the discontinuation criterion regarding serum potassium level was 0% (0 of 18) of subjects and 7.7% (1 of 13) of subjects, respectively. Thus, the risk of developing hyperkalaemia or meeting the discontinuation criterion regarding serum potassium is not necessarily high even if treatment with esaxerenone is continued without dose change after serum potassium level has increased to >5.0 mEq/L during treatment with esaxerenone. Also, all subjects who showed serum potassium level of ≥5.5 mEq/L were asymptomatic, and the increase was transient and the level returned to ≤5.0 mEq/L without dose change in most of them. Therefore, the applicant considers that the safety of patients regarding the increase in serum potassium level can be ensured if serum potassium level is measured at an appropriate timing and frequency according to the conditions of each patient and if the "Precautions for Dosage and Administration" section described in the package insert is followed, that is (1) if serum potassium level has increased to >5.0 mEq/L, the administration is continued without dose increase, (2) if serum potassium level subsequently increased to ≥5.5 mEq/L, the dose is reduced or the treatment is discontinued, and (3) if serum potassium level has increased to ≥6.0 mEq/L, the treatment is discontinued immediately.

PMDA instructed the applicant to specify the more appropriate frequency of serum potassium level measurement and the timing of measurement during administration of esaxerenone in the precautionary statement of the package insert (draft) by taking account of (1) the timing and frequency of serum potassium level measurement specified in the Japanese phase III study as well as the occurrences of serum potassium level of ≥5.5 mEq/L and their timings in the study, and (2) in Studies J203 and J301, the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L tended to be higher in the esaxerenone group than in the eplerenone group.

The applicant's explanation:
In Study J203 in which serum potassium level was measured at 1 week after the start of administration, only 1 subject in the esaxerenone 2.5 mg group showed serum potassium level of ≥5.5 mEq/L at 1 week after the start of administration. In this subject, the serum potassium level decreased to <5.5 mEq/L during continued administration, never increased again to ≥5.5 mEq/L. In Studies J301 and J302, periodical serum potassium measurement was started from 2 weeks after the start of administration. As

a result, in Study J301, subjects who showed serum potassium level of ≥5.5 mEq/L were observed more frequently at 2 weeks after the start of administration than at other measuring timepoints. Also, there were subjects who met the discontinuation criterion for serum potassium level at 2 weeks after the start of administration. The percentage of subjects who showed serum potassium level of ≥5.5 mEq/L at 2 weeks after the start of administration was 1.2% (1 of 84) of subjects in the esaxerenone 2.5 mg group and 0% (0 of 84) of subjects in the eplerenone group in Study J203; 1.5% (5 of 331) of subjects in the esaxerenone 2.5 mg group, 1.2% (4 of 338) of subjects in the esaxerenone 5 mg group, and 0.3% (1 of 332) of subjects in the eplerenone group in Study J301; and 0.8% (3 of 368) of subjects in Study J302. There were subjects whose serum potassium level was ≥5.5 mEq/L at 4 weeks after the start of administration. In Study J302, serum potassium level increased to ≥5.5 mEq/L in 11 subjects after dose increase of esaxerenone, and the increase in serum potassium level occurred at 2 weeks after dose increase in 1 subject and at 4 weeks after dose increase in 3 subjects. Although the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was higher in the esaxerenone group than in the eplerenone group in Studies J203 and J301, the above results suggest that it is possible to predict the extent of the increase in serum potassium level and occurrence of hyperkalaemia more appropriately by checking serum potassium level within 2 weeks after the start of administration (or after dose adjustment), thereby to prevent adverse events associated with the increase in serum potassium level. The long-term administration did not show any tendency of increase in the percentage of subjects showing serum potassium level of ≥5.5 mEq/L. However, since there were subjects who showed serum potassium level of ≥5.5 mEq/L at more than 2 weeks after the start of administration or dose increase, the following precautionary statement is included in the "Important Precautions" section in the package insert: Serum potassium level should be measured within 2 weeks after the start of administration (or after dose adjustment) and subsequent periodical measurements should be performed.

PMDA's view:
In clinical studies, the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was higher in the esaxerenone group than in the eplerenone group. Despite this observation, the applicant considers that esaxerenone is indicated also for patients with moderate renal impairment and diabetic patients with albuminuria or proteinuria. Therefore, the precautionary requirement regarding serum potassium level (e.g., frequency of measurement) should be comparable or stricter than that for eplerenone. In addition, taking account of the description in the package insert of eplerenone and the fact that patients with serum potassium level of ≥5.1 mEq/L were excluded from Studies J203, J301, and J302, PMDA considers that the applicant's proposal to contraindicate esaxerenone for patients with serum potassium level of ≥5.0 mEq/L at the start of administration is appropriate.

Among subjects in whom serum potassium level exceeded 5.0 mEq/L during the treatment period of clinical studies, there were a certain percentage of subjects who later showed serum potassium level of ≥5.5 mEq/L. Also, hyperkalaemia without symptoms is not necessarily safe. Therefore, in using esaxerenone in clinical practice, careful attention should be paid to an increase in serum potassium level even if it does not meet the discontinuation criterion, and dose reduction (or discontinuation if further dose reduction is infeasible) should be considered.

Regarding the frequency of serum potassium level measurement during treatment with esaxerenone, there were some subjects who showed serum potassium level of ≥5.5 mEq/L at 1 week after the start of treatment with esaxerenone. Nevertheless, the safety of esaxerenone could be ensured by measurement of serum potassium level at appropriate timing and frequency specified in clinical studies. PMDA therefore considers that the applicant's explanation to require serum potassium level measurement before the start of treatment with esaxerenone and within 2 weeks after the start of administration (or after dose adjustment) is appropriate. Since there were subjects who showed serum potassium level of ≥5.5 mEq/L at ≥4 weeks after the start of administration, suggesting changes in the renal function of patients, serum potassium level should be measured periodically during treatment with esaxerenone. Results of reviews in Sections 7.R.2.3 and 7.R.2.4 suggest the possibility that the risk of hyperkalaemia may increase not only in patients with moderate renal impairment and diabetic patients with albuminuria or proteinuria but also in elderly patients with a general tendency of renal impairment. The applicant's explanation to call for more frequent measurement of esaxerenone in these patient groups is appropriate.

Based on the above, the precautionary statement in the package insert regarding hyperkalaemia should be revised appropriately. The final conclusion will be made, also taking account of the comments raised in the Expert Discussion.

7.R.3.2 Concomitant use with ACE inhibitor or ARB

PMDA asked the applicant to explain the appropriateness of the cautionary statement regarding the concomitant use of esaxerenone with an ACE inhibitor or an ARB, based on the comparison of the incidences of adverse events between administration of esaxerenone with or without concomitant use with an ACE inhibitor or an ARB in clinical studies of esaxerenone.

The applicant's explanation:
Table 38 shows the incidences of adverse events in subjects receiving esaxerenone with or without concomitant use with an ACE inhibitor or ARB in Study J302, the study which allows such a comparison within the same clinical study among clinical studies of concomitant use of esaxerenone with an ACE inhibitor or an ARB. There was no clear difference in the incidences of adverse events, including serum potassium level of ≥5.5 mEq/L, between subjects with concomitant use with an ACE inhibitor or an ARB and subjects without concomitant use, which suggests it is appropriate to measure serum potassium level at the same frequency regardless of such concomitant use. However, since ACE inhibitors and ARBs are generally considered to have a risk of developing hyperkalaemia, it is necessary to alert physicians to possible increase in serum potassium level. Therefore, ACE inhibitors and ARBs are included in the "Precautions for Concomitant Use" section in the proposed package insert.

Table 38. Incidences of adverse events in subjects with concomitant use with ACE inhibitor or concomitant ARB and in subjects without concomitant use (safety analysis population)

	Up to Week 12 of administration of study drug		From Week 12 up to 52 of administration of study drug	
	Subjects without concomitant use (n = 304)	Subjects with concomitant use (n = 64)	Subjects without concomitant use (n = 283)	Subjects with concomitant use (n = 85)
Adverse events All adverse events	38.8 (118)	46.9 (30)	49.5 (140)	63.5 (54)
Serum potassium level ≥5.5 mEq/L ≥6.0 mEq/L once or ≥5.5 mEq/L twice in consecutive measurements	 3.0 (9) 0.7 (2)	 4.7 (3) 0 (0)	 2.8 (8) 0.7 (2)	 1.2 (1) 0 (0)

% (number of subjects)

PMDA's view:

Due to the small numbers of patients investigated in Study J302, there are limitations to compare the safety between subjects with or without concomitant use with ACE inhibitor or ARB, warranting caution in evaluating the results. Within these limitations, there was no marked difference in the incidence of adverse events between subjects with and without concomitant use, and there were no adverse events unique to subjects with concomitant use. Also, there was no clear difference in the percentage of subjects showing serum potassium level of ≥5.5 mEq/L between subjects with or without concomitant use with ACE inhibitor or ARB. On the other hand, given the mechanism of action of esaxerenone, there is a possibility that concomitant use of esaxerenone with an ACE inhibitor or an ARB, drugs which suppress the RA system, may increase the risk of hyperkalaemia. The applicant's explanation to raise caution against such risks is appropriate. The precautionary statement regarding concomitant use should be finalized, also taking account of comments raised in the Expert Discussion.

7.R.3.3 Concomitant use with potassium supplements

Concomitant use with potassium supplements is contraindicated in the treatment of hypertension with eplerenone, the drug in the same class. In addition, in Studies J203 and J301, the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was higher in the esaxerenone group than in the eplerenone group. Therefore, PMDA instructed the applicant to consider contraindicating the concomitant use with potassium supplements during the treatment with esaxerenone as well.

The applicant's explanation:

Potassium supplements are used mainly to improve hypokalaemia and associated symptoms. Taking account of the precautionary statement in the package insert of eplerenone, the drug in the same class, and the results of Studies J203 and J301, it is considered appropriate to contraindicate esaxerenone in patients who are receiving potassium supplements. On the other hand, a high proportion of patients with excess mineralocorticoid, such as patients with primary aldosteronism (PA), have hypokalaemia associated with the disease condition, and potassium supplement is sometimes administered before administration of MR antagonist in hypertensive patients with PA. In an open-label study (Study J307) which was conducted to investigate the efficacy and safety of esaxerenone administered to patients with PA at the starting dose of 2.5 mg with gradual dose increase up to 5 mg during 12 weeks, the concomitant use with potassium supplements was allowed and actually used in 5 of 44 subjects receiving esaxerenone. As a result of concomitant use with the potassium supplements by appropriately adjusting the dose, there were no subjects who showed serum potassium level of ≥5.0 mEq/L. From these results, it is considered

appropriate to allow concomitant use of esaxerenone with potassium supplements in patients with PA and patients with hypertension and hypokalaemia due to excess mineralocorticoid, the patient group listed with patients with PA in The Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2014 (the Japanese Society of Hypertension, 2014) although there is no use experience of esaxerenone in this patient group. Except in these patients, esaxerenone should be contraindicated in patients on treatment with potassium supplements.

PMDA's view:
When hypertensive patients are treated with eplerenone, the drug in the same class, the concomitant use with potassium supplements is prohibited to avoid the risk of developing hyperkalaemia regardless of the patient characteristics. In Studies J203 and J301, the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was higher in the esaxerenone group than in the eplerenone group. In Study J307, only 5 subjects received esaxerenone in combination with potassium supplement. Thus, it cannot be concluded that potassium supplements is safe to be concomitantly administered solely based on these results. Taking account of these results and the mechanism of action of esaxerenone, it is considered appropriate to contraindicate the concomitant use with potassium supplements to ensure the safety of patients, as is the case with eplerenone, the drug in the same class. The precautionary statement regarding concomitant use with potassium supplements will be further discussed, also taking account of comments raised in the Expert Discussion.

7.R.3.4 Risk of decreased renal function

PMDA asked the applicant to explain the possibility of renal impairment associated with esaxerenone and the necessity of raising caution against such a risk.

The applicant's explanation:
In Studies J203 and J301, the mean change from baseline in eGFR in the esaxerenone 5 mg group was −6.36 mL/min/1.73 m^2 and −5.55 mL/min/1.73 m^2, respectively, at 12 weeks after the start of administration, showing a decrease from the baseline value, while no clear change was observed either in the placebo group or eplerenone group. From 4 weeks after the start of administration, eGFR in the esaxerenone group remained at an almost constant level, albeit lower than the baseline value, and generally returned to the baseline value after the end of administration of esaxerenone, suggesting that the change is reversible. In Study J302 as well, eGFR remained almost at a constant level from Week 12 to 52 in the treatment period, albeit at a lower level than the baseline value. Only a few subject experienced decreased renal function or adverse events associated with decreased renal function. Although there are limitations to the discussion of factors prone to develop decreased renal function, the characteristics (age, sex, body weight, concurrent illness, concomitant drugs, eGFR during the observation period) of subjects who experienced decreased renal function or associated adverse events in each study were not significantly different from those in the entire subject population, in each study. All of the observed adverse events associated with decreased renal function were mild in severity, did not require intervening treatments, and eventually resolved or improved. Therefore, no further precautions are necessary against the risk of decreased renal function in addition to renal dysfunction, etc. described in the "Other adverse reactions" section of the package insert (draft).

PMDA's view:
In clinical studies, the decrease in eGFR tended to be greater in the esaxerenone group than in the placebo and eplerenone groups, suggesting a possibility of decreased renal function associated with esaxerenone, warranting caution. Given that decreased renal function may lead to the occurrence of hyperkalaemia and that, in clinical studies, the percentage of subjects showing serum potassium level of ≥5.5 mEq/L was higher in the esaxerenone group than in the eplerenone group, it is important during administration of esaxerenone to monitor renal function which is closely related to electrolyte levels. However, hyperkalaemia-related risks are controllable by advising to measure serum potassium level frequently [see Section "7.R.3.1 Hyperkalaemia"]. Thus, PMDA considers it appropriate that the applicant does not require a further precautionary statement regarding the risk of decreased renal function provided that appropriate measures are taken according to the renal function [see Section "7.R.2.3 Administration to patients with moderate renal impairment"]. On the other hand, renal dysfunction, once manifest, may lead to a serious outcome. After marketing, it is expected that esaxerenone is used by patients with more diverse characteristics regarding renal function and renal diseases than patients enrolled in the clinical studies for this approval application. Therefore, it is necessary to collect post-marketing information on the risk of decreased renal function associated with esaxerenone.

7.R.3.5 Hypotension and excessive blood pressure decrease

Taking account of the results of the clinical studies, PMDA asked the applicant to explain the necessity of raising caution against hypotension and excessive blood pressure decrease associated with esaxerenone.

The applicant's explanation:
The incidence of hypotension-related adverse events (blood pressure decreased, hypotension, or orthostatic hypotension) was 0.3% (1 of 368) of subjects in Study J302 and 1.7% (1 of 58) of subjects in Study J305 for orthostatic hypotension. All of the adverse events were mild and resolved without intervening treatment. Hypotension was not observed in Studies J203 and J301. The incidence of hypotension-associated symptoms (cervicogenic vertigo, dizziness postural, vertigo CNS origin, dizziness, or dizziness exertional) in Study J203 was 1.1% (1 of 87) of subjects in the placebo group, 0% (0 of 83) of subjects in the esaxerenone 1.25 mg group, 2.4% (2 of 84) of subjects in the esaxerenone 2.5 mg group, and 2.3% (2 of 88) of subjects in the esaxerenone 5 mg group, being similar between the esaxerenone groups and placebo group. In Study J301, the incidence was 0.6% (2 of 331) of subjects in the esaxerenone 2.5 mg, 0.6% (2 of 338) of subjects in the esaxerenone 5 mg, and 0% (0 of 332) of subjects in the eplerenone group, showing no dose dependency in the occurrence of hypotension-related symptoms associated with esaxerenone. The incidence of hypotension-related symptoms was 1.9% (7 of 368) of subjects in Study J302, showing no tendency of increase with long-term administration. The incidence was 3.4% (2 of 58) of subjects in Study J305 and 2.0% (1 of 51) of subjects in Study J306. Among hypotension-related symptoms observed in clinical studies, 1 event was moderate in severity but resolved after discontinuation of esaxerenone administration. All other symptoms were mild and resolved with or without intervening treatment with drugs. There was no tendency of increased incidence in any specific population although there are limitations to the discussions on the characteristics of subjects because of the limited number of subjects who experienced hypotension-related adverse events.

Thus, most of the hypotension and hypotension-related symptoms observed were mild, posing no significant concern for safety related to hypotension or excessive blood pressure decrease. Therefore, it is unnecessary to raise precaution against blood pressure decrease, except the general precaution against excessive blood pressure decrease in elderly patients.

PMDA's view:
The incidence of hypotension and hypotension-associated adverse events observed in clinical studies did not show any clear tendency of increase in the esaxerenone group compared with the placebo group and the eplerenone group, and neither a long-term administration nor any specific patient group suggested an increased risk of excessive decrease in blood pressure. Therefore, the applicant's explanation to include a precaution against excessive blood pressure decrease in the elderly patients, as is the case with common hypotensive drugs, is appropriate. On the other hand, the possibility cannot be excluded that excessive blood pressure decrease occurs with the mechanism of action of esaxerenone. Since it is expected that esaxerenone, after marketing, is used by a wider variety of patients than the patient population in clinical studies conducted for this approval application, it is necessary to collect post-marketing information on the risk of decreased blood pressure associated with esaxerenon from a wide range of patient populations.

7.R.3.6 Sex hormone-associated adverse events

The applicant's explanation about sex-associated adverse events:
The incidence of sex hormone-associated adverse events[2)] observed in each clinical study was benign prostatic hyperplasia in 0.3% (1 of 331) of subjects in the esaxerenone 2.5 mg group in Study J301; dysmenorrhoea in 0.3% (1 of 368) of subjects, prostatitis in 0.3% (1 of 368) of subjects, and adenomyosis in 0.3% (1 of 368) of subjects in Study J302; prostatitis in 1.7% (1 of 58) of subjects in Study J305; and menorrhagia in 2.3% (1 of 44) of subjects, and genital haemorrhage in 2.3% (1 of 44) of subjects in Study J307. No sex hormone-associated adverse events were observed in other studies. Among these adverse events observed in 7 subjects, events assessed as causally related to the study drug were benign prostatic hyperplasia observed in Study J301 and menorrhagia observed in Study J307, but both events were mild in severity and resolved with or without treatment with a therapeutic agent while administration of the study drug was continued. Based on the above, administration of esaxerenone is unlikely to cause sex hormone-associated adverse events, precluding the necessity of raising caution against sex hormone-associated adverse events.

PMDA's view:
Spironolactone, the MR antagonist approved in Japan, is reported to cause sex hormone-associated adverse events such as gynaecomastia in men. Since there are no clinical data that directly compared esaxerenone and spironolactone, caution is required in interpreting available data. Nevertheless, taking account of the following, the applicant's explanation not to give any specific cautionary statement in the package insert is appropriate.

- Currently, available clinical study data do not suggest any tendency of developing sex hormone-associated adverse events with esaxerenone.

2) MedDRA SOC "Reproductive system and breast disorders"

- Esaxerenone is shown to be more highly selective to MR than spironolactone [see Section "3.R.1 Effect on hypertension"].
- Similar to esaxerenone, eplerenone, which is considered to be more selective to MR than spironolactone, seldom causes sex hormone-associated adverse drug reactions (The Japanese Society of Hypertension Guidelines for the Management of Hypertension, 2014 [The Japanese Society of Hypertension, 2014]).

7.R.3.7 Treatment with esaxerenone in patients with hepatic impairment

Taking account of the results of the clinical studies, PMDA asked the applicant to explain the appropriateness of giving cautionary statement in treatment with esaxerenone in patients with hepatic impairment.

The applicant's explanation:

Incidences of adverse events were investigated in subgroups classified by hepatic function (parameters during the observation period: AST ≥40 U/L or <40 U/L, ALT ≥45 U/L or <45 U/L). Among subjects in the esaxerenone group, the percentage of those with AST ≥40 U/L or ALT ≥45 U/L was 5.1% (13 of 255) of subjects and 9.0% (23/255) of subjects, respectively, in Study J203; 7.0% (47/669) of subjects and 11.1% (74/669) of subjects in Study J301; and 7.6% (28 of 368) of subjects and 11.1% (41 of 368) of subjects in Study J302. The incidence of all adverse events, the incidence of hepatic function-related adverse events, and the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L were compared for subgroups classified by hepatic function. Results showed no clear difference between the subgroups although there were limitations to the interpretation due to a large difference in the number of subjects between the subgroups. Based on the above, esaxerenone is unlikely to pose any higher risk in patients with hepatic impairment. However, taking account of the facts that no clinical study was conducted on patients with severe hepatic impairment and that since esaxerenone is metabolized in the liver, the possibility cannot be excluded that blood concentration of esaxerenone is elevated in patients with severe hepatic impairment. Careful administration should be recommended in patients with severe hepatic impairment to raise cautions.

PMDA's view:

No clear effect on the exposure to esaxerenone was observed in patients with mild or moderate hepatic impairment [see Section "6.R.1 Administration to patients with hepatic impairment]. Also, there are no clinical data suggestive of any increase in the incidence of adverse events in subjects with hepatic impairment. However, taking account of the facts that patients with severe hepatic impairment were not enrolled in clinical studies and that esaxerenone is metabolized in the liver, the applicant's explanation that careful administration should be recommended in patients with severe hepatic impairment to raise cautions is appropriate. It is necessary to collect post-marketing information on the incidences of adverse reactions in patients with severe hepatic impairment receiving esaxerenone.

7.R.3.8 Treatment with esaxerenone in the elderly

PMDA instructed the applicant to explain the efficacy and safety of esaxerenone in the elderly and the necessity of starting the administration from 1.25 mg, the low dose.

The applicant's explanation about treatment with esaxerenone in the elderly:
In Studies J203 and J301, no difference was noted in the incidence of adverse events (including those of hypotension and renal dysfunction) between elderly (≥65 years old) and non-elderly (<65 years old) subjects in the esaxerenone group, and there were no clear safety problems in elderly subjects aged ≥75 years. The percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was 1.6% (3 of 189) of subjects aged <65 years, 3.0% (2 of 66) of subjects aged ≥65 years, and 0% (0 of 7) of subjects aged ≥75 years in Study J203. In Study J301, the percentage was 4.1% (11 of 270) of subjects aged <65 years, 6.6% (4 of 61) of subjects aged ≥65 years, and 42.9% (3 of 7) of subjects aged ≥75 years in the esaxerenone 2.5 mg group; 2.8% (8 of 283) of subjects aged <65 years, 3.6% (2 of 55) of subjects aged ≥65 years, and 0.0% (0 of 10) of subjects aged ≥75 years in the esaxerenone 5 mg group. In Study J302, the percentage was 5.2% (15 of 290) of subjects aged <65 years, 6.4% (5 of 78) of subjects aged ≥65 years, and 0% (0 of 6) of subjects aged ≥75 years. In the esaxerenone 2.5 mg group of Study J301, the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L was high in subjects aged ≥75 years, but this was likely to be an accidental result due to the small number of subjects studied, judging from the observations that there were no subjects aged ≥75 years who showed serum potassium level of ≥5.5 mEq/L in the esaxerenone 5 mg group of Study J301 or in Studies J203 or J302. Based on the above, the applicant considers that there is no clear difference in the incidence of hyperkalaemia in the esaxerenone group among different age groups. In Study J305, the percentage of subjects who showed serum potassium level of ≥5.5 mEq/L tended to be higher in subjects aged ≥65 years and in subjects aged ≥75 years than subjects aged <65 years. However, the package insert (draft) states that treatment with esaxerenone in patients with moderate renal impairment should be started from the low dose (1.25 mg) regardless of age, and no significant safety problems were noted in subjects including the elderly in the clinical study conducted using the same recommendation. Furthermore, the package insert recommends careful administration in the elderly regardless of moderate renal impairment. Therefore, it is unnecessary to start esaxerenone from the low dose (1.25 mg) in all elderly patients.

PMDA's view:
Only a limited number of elderly subjects, subjects aged ≥75 years in particular, were enrolled in clinical studies, precluding accurate comparison of safety between elderly and non-elderly subjects. Nevertheless, the clinical study data do not suggest any clear tendency of increased risk in the elderly subjects compared with the non-elderly subjects. Therefore, PMDA considers it unnecessary to start administration of esaxerenone from the low dose (1.25 mg), merely for reason of advanced age. Also, taking account of the fact that elderly people generally have reduced renal function and are prone to develop hyperkalaemia and that excessive blood pressure decrease is undesirable in this patient group (The Japanese Society of Hypertension Guidelines for the Management of Hypertension, 2014 [The Japanese Society of Hypertension, 2014]), PMDA concludes that the applicant's explanation to require careful administration is acceptable.

7.R.4 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:
In order to investigate the incidences of hyperkalaemia (including the confirmation of safety in patients with renal impairment, safety in diabetic patients with albuminuria or proteinuria, and safety in concomitant use with potassium supplements), the applicant plans to conduct a post-marketing database

surveillance. Incidences of hypotension-related events and renal dysfunction will be monitored by the usual pharmacovigilance activities.

PMDA's view:
On the basis of the submitted clinical data and the review, etc., in Section 7.R.3, that it is necessary to collect information on hyperkalaemia, hypotension-related events, occurrences of renal dysfunction, safety in patients with renal impairment, and safety in diabetic patients with albuminuria or proteinuria, by appropriate post-marketing pharmacovigilance activities. A final decision on the appropriateness of the specifications for post-marketing investigations and of the method for collecting information will be made, taking account of comments raised in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-2, CTD 5.3.5.2-1, CTD 5.3.5.2-3, CTD 5.3.5.2-4, CTD 5.3.5.2-6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that esaxerenone has efficacy in the treatment of patients with hypertension. As for safety, although particular caution is required against the occurrence of hyperkalaemia, it is generally manageable and esaxerenone has acceptable safety in view of its benefits, provided that patients are selected and a blood test is conducted appropriately. Esaxerenone provides a new treatment option for patients with hypertension and thus has clinical significance. Further discussions are needed for precautionary statements in the package insert and specifications for post-marketing investigations.

PMDA has concluded that esaxerenone may be approved if esaxerenone is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 8, 2018

Product Submitted for Approval

Brand Name	Minnebro Tablets 1.25 mg Minnebro Tablets 2.5 mg Minnebro Tablets 5 mg
Non-proprietary Name	Esaxerenone
Applicant	Daiichi Sankyo Company, Limited
Date of Application	February 26, 2018

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on Section "7.R.1 Clinical positioning and indication," Section "7.R.2 Efficacy and dosage and administration," and Section "7.R.3 Safety" in Review Report (1), except issues on hyperkalaemia discussed in Section 1.1.

PMDA also discussed the following points and took action as necessary.

1.1 Hyperkalaemia

The expert advisors supported the PMDA's conclusion that dose reduction (or discontinuation if further dose reduction is infeasible) should be considered even if the increased serum potassium level during treatment with esaxerenone does not meet the discontinuation criterion. The expert advisors also supported the PMDA's conclusion that the test for serum potassium levels should be performed more frequently in patients with an increased risk of hyperkalaemia, such as patients with moderate renal impairment, diabetic patients with albuminuria or proteinuria, and patients receiving ACE inhibitor or ARB in combination, but some advisors commented that the term "more frequently" should be specifically described, whereas others commented that a rough guide for the frequency would suffice to allow flexibility and adjust to the patient's condition. Discussions were held on the basis of these comments, the frequency of serum potassium test in Studies J203, J301, J302, J305, and J306, and precautionary statements for drugs in the same class. The discussion finally reached the conclusion that

the precautionary statements provided as shown below are appropriate at this point and that the frequency of the test and the patient populations requiring precautions should be reviewed appropriately based on the results of the post-marketing surveillance, etc.

Precautions for Dosage and Administration

1. During administration of esaxerenone, the dose reduction should be considered if serum potassium level increases to >5.0 mEq/L, the dose should be reduced or the treatment should be discontinued if serum potassium level increases to ≥5.5 mEq/L, and the treatment should be discontinued immediately if serum potassium level increases to ≥6.0 mEq/L.

2. In patients with moderate renal impairment (eGFR, ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) and diabetic patients with albuminuria or proteinuria, treatment with esaxerenone should be started from administration of 1.25 mg once daily and, depending on the serum potassium level and patient's conditions, the dose should be increased to 2.5 mg once daily at ≥4 weeks after the start of administration. The dose may be increased to 5 mg in patients whose blood pressure is not adequately controlled.

Important Precautions

1. Hyperkalaemia may occur. In principle, serum potassium level should be measured before the start of administration, once within 2 weeks and approximately 1 month after the start of administration (or after the dose adjustment), and periodically thereafter. The risk of developing hyperkalaemia may increase particularly in patients with moderate renal impairment, diabetic patients with albuminuria or proteinuria, elderly patients, and patients who are also taking drugs that are prone to induce hyperkalaemia. More frequent measurement is required in these patients.

(The rest is omitted.)

The expert advisors supported PMDA's conclusion that concomitant use with potassium supplements should be contraindicated as is the case with eplerenone, the drug in the same class.

1.2 Risk management plan (draft)

In view of the discussions in Section "7.R.4 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for esaxerenone should include the safety specifications presented in Table 39, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 40. As for pharmacovigilance activities using Medical Information Database, the optimal method should be further investigated by taking account of the feasibility.

Table 39. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hyperkalaemia • Hypotension-related events	• Renal dysfunction	• Safety in patients with renal impairment • Safety in diabetic patients with albuminuria or proteinuria
Efficacy specification		
Not applicable		

Table 40. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey (hyperkalaemia)	• Disseminate information based on the early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals (guide for proper use of esaxerenone) • Organize and disseminatematerials for patients (patient information leaflet on esaxerenone)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product, and neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Hypertension

Dosage and Administration

The usual adult dose is 2.5 mg of esaxerenone administered orally once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 5 mg.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

A→B	From apical surface to basolateral surface
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Androgen receptor
ARB	Angiotensin II receptor blocker
ARC	Active renin concentration
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve of the analyte in plasma
AUC_{0-24}	AUC from 0 to 24 hours after administration
AUC_{∞}	AUC from 0 hour after administration to infinity
AUC_{last}	AUC from 0 hour after administration to the last quantifiable time
AUC_{ss}	AUC under the steady state
AUC_{t}	AUC from 0 hour after administration to the time of the last sampling
B→A	From basolateral surface to apical surface
BA	Bioavailability
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BE Guideline for different strength	"Amendments to the Guideline for Bioequivalence Studies of Generic Products and Other Guidelines," PFSB/ELD Notification No. 0229-(10), dated February 29, 2012, Attachment 2: Guidelines for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms
BE Guideline for formulation change	"Amendments to the Guideline for Bioequivalence Studies of Generic Products and Other Guidelines," PFSB/ELD Notification No. 0229-(10), dated February 29, 2012, Attachment 3: Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms
CCB	Calcium channel blocker
Ccr	Creatinine clearance
CHL	Chinese hamster lung
CI	Confidence interval
CK	Creatine phosphokinase
CL	Total body clearance
CL/F	Apparent total body clearance
C_{max}	Maximum concentration of analyte in plasma
CPP	Critical process parameter
CQA	Critical quality attribute
CRE	Creatinine
C_{trough}	Trough concentration of analyte in plasma
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMSO	Dimethyl sulfoxide
DN	Diabetic nephropathy
eGFR	Estimated glomerular filtration rate
esaxerenone	esaxerenone
FAS	Full analysis set
GC	Gas chromatography
GR	Glucocorticoid receptor
hERG	Human ether-á-go-go related gene

[redacted]	[redacted]
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH M7 Guideline	"Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (PSEHB/ELD Notification No. 1110-3, dated November 10, 2015)
ICH Q1E Guideline	"Guideline on the Evaluation for Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3 2003)
IR	Infrared absorption spectrum
ka	Absorption rate constant
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
LOCF	Last observation carried forward
LSC	Liquid scintillation counter
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
Minnebro	Minnebro tablets
MR	Mineralocorticoid receptor
mRNA	Messenger ribonucleic acid
MS	Mass spectrum
[redacted]	[redacted]
Na^+/K^+	Sodium ion/potassium ion
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance spectrum
NZW	New Zealand white
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PA	Primary aldosteronism
PAC	Plasma aldosterone concentration
P_{app}	Apparent permeability coefficient
PD	Pharmacodynamics
PE	Polyethylene
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Polypropylene
PPK	Population pharmacokinetics
PPS	Per protocol set
PR	Progesterone receptor
PRA	Plasma renin activity
PTP	Press through packaging
QbD	Quality by Design
RA	Renin angiotensin
[redacted]	[redacted]
SBP	Systolic blood pressure
SD rat	Sprague-Dawley rat
SMQ	Standardised MedDRA query
SOC	System organ class
$T_{1/2}$	Half-life
T-BIL	Total bilirubin
TG	Triglyceride

T_{max}	Time to reach the maximum plasma concentration
UACR	Urine albumin-to-creatinine ratio
UDPGA	Uridine 5'-diphosphoglucuronic acid
UGT	Uridine 5'-diphosphate-glucuronosyltransferase
UV/VIS	Ultraviolet-visible spectrum
V_c	Distribution volume of the central compartment
V_{ss}	Distribution volume under the steady state
γ-GTP	γ-glutamyl transferase
^{3}H-aldosterone	D-[1,2,6,7-3H(N)]-aldosterone