Report on the Deliberation Results

December 13, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Pivlaz I.V. Infusion Liquid 150 mg
Non-proprietary Name	Clazosentan Sodium (JAN*)
Applicant	Idorsia Pharmaceuticals Japan Ltd.
Date of Application	March 1, 2021

Results of Deliberation

In its meeting held on November 26, 2021, 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. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

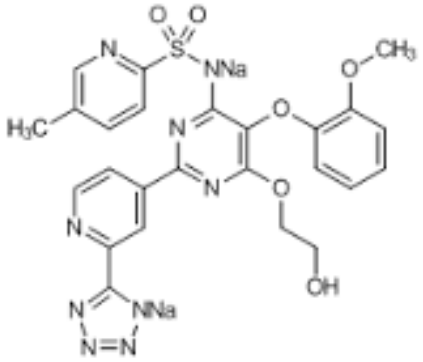
Review Report

November 17, 2021
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	Pivlaz I.V. Infusion Liquid 150 mg
Non-proprietary Name	Clazosentan Sodium
Applicant	Idorsia Pharmaceuticals Japan Ltd.
Date of Application	March 1, 2021
Dosage Form/Strength	Injection: Each vial contains 150 mg of clazosentan.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{25}H_{21}N_9Na_2O_6S$

Molecular weight: 621.54

Chemical name: Disodium {6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1*H*-tetrazol-1-id-5-yl)pyridine-4-yl]pyrimidin-4-yl}(5-methylpyridine-2-ylsulfonyl)azanide

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 prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes, 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 approval condition. The occurrence of the following events should be further investigated: fluid retention, haemorrhage intracranial, hypotension/blood pressure decreased, anaemia/haemoglobin decreased, hepatic function abnormal, tachyarrhythmia (ventricular and supraventricular arrhythmias including QT prolongation).

Indication

Prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes

Dosage and Administration

The usual adult dosage is 300 mg (12 mL) of clazosentan diluted with 500 mL of physiological saline, continuously administered intravenously at the speed of 17 mL/h (clazosentan 10 mg/h) using a constant infusion pump. Administration of clazosentan is started early after surgery for subarachnoid haemorrhage and continued until Day 15 after the onset of subarachnoid haemorrhage. The dose may be reduced depending on the liver function and concomitant medications.

Approval Condition

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

Attachment

Review Report (1)

September 21, 2021

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	Pivlaz for I.V. Infusion 150 mg (to be changed to Pivlaz I.V. Infusion Liquid 150 mg)
Non-proprietary Name	Clazosentan Sodium
Applicant	Idorsia Pharmaceuticals Japan Ltd.
Date of Application	March 1, 2021
Dosage Form/Strength	Injection: Each vial contains 150 mg of clazosentan.

Proposed Indication

Prevention of cerebrovascular spasm after treatment of subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes

Proposed Dosage and Administration

The usual adult dosage is 300 mg of clazosentan (two 6-mL vials) diluted with 500 mL of physiological saline, continuously administered intravenously at the speed of 17 mL/h (clazosentan 240 mg/24 h) using a constant infusion pump immediately after preparation. Administration of clazosentan is started early after treatment of subarachnoid haemorrhage and continued until Day 15 after the onset of subarachnoid haemorrhage.

Table of Contents

List of Abbreviations

See Appendix.

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

Among patients with aneurysmal subarachnoid hemorrhage (aSAH), 40% to 70% of them experience cerebrovascular spasm 4 to 14 days after the onset of aSAH (*CNS Neurosci Ther.* 2019;25:1096-112). Further, 17% to 40% of patients with cerebrovascular spasm present with delayed ischemic neurological deficit (DIND), and approximately half of patients with DIND progress to cerebral infarction (*Neurosurg Rev.* 2007;30:22-30). The onset of cerebrovascular spasm is related to the onset of cerebral infarction and poor prognosis (*Stroke.* 2011;42:919-23). Thus, prevention and treatment of cerebrovascular spasm are important in patients with aSAH.

Clazosentan sodium (hereinafter referred to as "clazosentan"), an endothelin receptor antagonist (ERA) discovered by Actelion, is a highly selective inhibitor of endothelin A (ET_A) receptor. It is considered to prevent cerebral vasoconstriction caused by high level endothelin-1 (ET-1) induced by subarachnoid hemorrhage (SAH), thereby contributing to the prevention of cerebrovascular spasm.

Outside Japan, the clinical development of clazosentan was initiated by Vanguard Medica Ltd. in [redacted]. As of August 2021, a phase III study of clazosentan is ongoing for the same indication as that proposed for the present application. Clazosentan has not been approved in any country or region.

In Japan, the clinical development of clazosentan was started in 20[redacted] by Actelion Pharmaceuticals Japan Ltd. (currently Janssen Pharmaceutical K.K.). The applicant has filed a marketing application, with the proposed indication of "Prevention of cerebrovascular spasm after treatment of subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes," based on data including those from Japanese clinical studies in patients who underwent clipping or coiling for aSAH.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale yellow crystals or crystalline powder. Its description, melting point, partition coefficient, solubility, dissociation constant, and hygroscopicity have been determined. The drug substance is present in a total of 5 crystalline forms (crystalline forms [redacted], [redacted], [redacted], [redacted], and [redacted]). In the commercial-scale production process, only crystallin form [redacted], which is [redacted] and [redacted], is formed and stable at room temperature.

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

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as the starting materials. Synthesizing processes of [redacted], [redacted], [redacted], [redacted], and [redacted]

were identified as the critical steps. [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description (appearance), identification (IR, high performance liquid chromatography [HPLC], qualitative tests), purity (related substances [HPLC], residual solvents [gas chromatography (GC)]), water content, microbial limits, bacterial endotoxins, and assay (clazosentan sodium [HPLC], [redacted] [potentiometric titration]).

2.1.4 Stability of drug substance

Table 1 shows main stability studies conducted on the drug substance. The drug substance was shown to be stable. Also, a photostability testing showed that the drug substance was photostable.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 production scale batches	30°C	65% RH	Double polyethylene bag + aluminum bag + metallic drum	24 months
Accelerated		40°C	75% RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance stored at room temperature in the double polyethylene bag placed in an aluminum bag and in a metallic drum, in accordance with the ICH Q1E Guidelines. Long-term testing will be continued for 60 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection containing 161.4 mg of the drug substance (150 mg of clazosentan) in each vial (6 mL). The drug product contain excipients: trometamol, disodium edetate hydrate, sodium chloride, hydrochloric acid, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through weighing/dissolving, [redacted], [redacted], depyrogenation of vial, sterilization of closure system, sterile filtration, [redacted], clamping, final sterilization, test, and packaging/labeling. [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as the critical steps. In-process control parameters and control values were defined in the critical steps and in [redacted], [redacted], and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (HPLC/ultraviolet spectroscopy [UV]), pH, purity (related substances [HPLC]), [redacted] (HPLC), bacterial endotoxins, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows the main stability studies performed on the drug product. The drug product was shown to be stable. A photostability testing showed that the drug product was photostable.

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Colorless glass vial + butyl rubber stopper + aluminum seal	24 months
	3 commercial-scale batches				36 months
Accelerated	6 commercial-scale batches	40°C	75% RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product stored at room temperature in a colorless glass vial with a butyl rubber stopper and a flip-off aluminum seal. Long-term testing will be continued for 60 months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

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

In this section, the dose of clazosentan sodium is expressed as the equivalent dose of clazosentan.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies (CTD 4.2.1.1.1)

3.1.1.1 Binding affinity to human ET_A and ET_B receptors

The inhibitory effect of clazosentan against the binding of ^{125}I-labeled ET-1 (32 pmol/L) to human ET_A or ET_B receptor was investigated using microsomal membrane preparations from African green monkey kidney (COS-1) cell engineered to express human ET_A or endothelin B (ET_B) receptor. Inhibition constant (K_i) value (mean ± standard error [SE]) of clazosentan against ET_A and ET_B receptors was 0.6 ± 0.3 nmol/L and 1930 ± 340 nmol/L, respectively.

3.1.1.2 Effect on ET_A or ET_B receptor-mediated ET-1 functions

3.1.1.2.1 Effect on intracellular signal transduction

The inhibitory effect of clazosentan (0.01-10000 nmol/L) against ET-1 (10 nmol/L)-induced production of ^{3}H-labeled inositol triphosphate was investigated using COS-1 cells engineered to express human ET_A or ET_B receptor. Half maximal inhibitory concentration (IC_{50}) of clazosentan against ET_A and ET_B receptors was 5 nmol/L and 3000 nmol/L, respectively.

The inhibitory effect of clazosentan (0.01-10000 nmol/L) against ET-1 (10 nmol/L)-induced calcium ion influx was investigated using human embryonic kidney (HEK)293 cells engineered to co-express human ET_A or ET_B receptor and calcium-sensitive photoprotein (aequorin). IC_{50} (mean ± standard deviation [SD]) of clazosentan against ET_A and ET_B receptor was 0.23 ± 0.1 nmol/L and 422 ± 450 nmol/L, respectively.

3.1.1.2.2 Effect on ET-1-induced contraction of isolated tissues

Using isolated rat aortas, the inhibitory effect of clazosentan (300-3000 nmol/L) against ET-1 (0.01-1000 nmol)-induced contraction was investigated. The negative logarithm of the molar

concentration of antagonist that causes a 2-fold shift to the right of an agonist concentration-response curve (pA_2) was 9.5.

Using isolated rat tracheal rings, the inhibitory effect of clazosentan (300-3000 nmol/L) against the contraction induced by sarafotoxin (SRTX) S6c (0.1-1000 nmol/L), a selective ET_B receptor agonist, was investigated. pA_2 was 6.4.

3.1.2 *In vivo* studies

3.1.2.1 Effect on peripheral vasoconstriction in normal animals (CTD 4.2.1.1.1)

Clazosentan (0.01, 0.1, 1, or 3 mg/kg) or vehicle (physiological saline) was administered intravenously to pithed normotensive rats (n = 4-5/group) under anesthesia and, 5 minutes later, ET-1 precursor (big ET-1) was administered intravenously using a gradual dose escalation regimen, and peripheral blood pressure was measured. Clazosentan suppressed a big ET-1-induced mean arterial blood pressure (MAP) increase by up to 80% in a dose-dependent manner, with the ID_{50} (the dose that causes 50% inhibition) of 0.05 mg/kg. Clazosentan had no effect on MAP before administration of big ET-1.

3.1.2.2 Effect on cerebrovascular spasm in SAH (CTD 4.2.1.1.1, 4.2.1.1.3, and 4.3.8)

Animal models of post-SAH cerebrovascular spasm were generated by injecting the autologous blood into the cisterna magna, thereby causing vasoconstriction of the basilar artery (*Neurosurgery.* 1995;37:78-85, *Neurosurgery.* 1995;37:87-90).

(a) Prophylactic administration

Clazosentan (4 or 10 mg/kg/dose) or vehicle (physiological saline) was administered intravenously twice daily for 4 days to male or female dogs (n = 5-12/group) that had received autologous blood injection into the cisterna magna on Day 1. The cross-sectional area of the basilar artery was measured 4 hours after the last dose on Day 4. In the vehicle group, the area decreased by 40% ± 9% (mean ± SE) from the area before autologous blood injection. In the clazosentan 4 mg/kg group, the area decreased by 36% ± 10%, which was not significantly different from the decrease in the vehicle group. In the clazosentan 10 mg/kg group, the area decreased by only 3% ± 7%, showing a suppression of the decrease in the cross-sectional area of the basilar artery compared with the vehicle group.

(b) Therapeutic administration

On Day 1 and Day 2, the autologous blood was injected into the cisterna magna of male and female dogs (n = 5-6/group). On Day 4, clazosentan (0.3, 1, or 3 mg/kg) or vehicle (physiological saline) was administered intravenously under anesthesia, followed by continuous intravenous administration of clazosentan (0.6, 2, or 6 mg/kg) or vehicle (physiological saline) for 2 hours (total dose of 0.9, 3, or 9 mg/kg, respectively). The cross-sectional area of the basilar artery was measured every 30 minutes for 2 hours after the start of administration. The cross-sectional area before the study drug administration on Day 4 (baseline) decreased by 65% ± 1% (mean ± SE) from the area before autologous blood injection into the cisterna magna. The cross-sectional area of the basilar artery then increased in a dose-dependent manner; the area in the clazosentan 9 mg/kg group increased by 47% ± 16% from baseline to 2 hours after the start of administration. A significant difference was observed in

the ratio of change in the cross-sectional area of the basilar artery in all clazosentan groups compared with the vehicle group.

The autologous blood was injected into the cisterna magna of male and female rabbits (n = 4-6/group) and, 48 hours later, clazosentan (10 mg/kg) or vehicle (physiological saline) was administered intravenously under anesthesia. The cross-sectional area of the basilar artery was measured 30 and 60 minutes after the administration. When the area measured after intravertebral arterial injection of papaverine at the end of the study was considered as 100% (at maximum expansion), the area in the clazosentan group was 89%, which was higher than that (42%) in the vehicle group.

3.2 Secondary pharmacodynamics

3.2.1 Effect on receptors (CTD 4.2.1.2.1 and 4.2.1.2.2)

The inhibitory effect of clazosentan (1 μmol/L) against 55 types of receptors was investigated by radioligand binding studies. Clazosentan did not inhibit the ligand binding of any receptor by ≥30% except endothelin (ET) receptor.

3.3 Safety pharmacology

Table 3 shows the results of safety pharmacology studies.

Table 3. Summary of safety pharmacology studies

Organ system	Test system	Endpoint and method	Dose	Route of administration	Findings	CTD
Central nervous system	CD-1 mice (n = 6 males/group)	Irwin method	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.1
	CD-1 mice (n = 10 males/group)	Suppression of convulsion induced by pentylenetetrazole	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.2
	CD-1 mice (n = 10 males/group)	Induction of convulsion induced by pentylenetetrazole	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	
	SD rats (n = 10 males/group)	Nociceptive pain	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.3
	SD rats (n = 8 males/group)	Arousal, muscular tonicity, and motor coordination	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.4
	CD-1 mice (n = 6/group)	Hexobarbital-induced sleep	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.5
	CD-1 mice (n = 10 males/group)	Body temperature	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	3 mg/kg group: Low deep body temperature	4.2.1.3.6
Cardiovascular system	hERG-transfected HEK293 cells (3 specimens each)	Potassium ion current	0,[b] 10, 30, 100, 300 µmol/L	*In vitro*	No effect	4.2.1.3.7
	Beagle dogs (n = 3/sex)	Arterial blood pressure, heart rate	0,[c] 0.001, 0.01, 0.25, 1, 4 mg/kg/h 24-hour continuous administration[d]	i.v.	≥0.01 mg/kg/h: Decreased MAP, increased heart rate	4.2.1.3.11
	Göttingen minipigs (n = 3/sex)		0,[c] 0.1, 0.5, 1, 2, 4, 8 mg/kg/h 24-hour continuous administration[e]	i.v.	≥0.1 mg/kg/h: Decreased MAP	4.2.1.3.8
	Beagle dogs (n = 4/group)		(a) 0,[c] 1, 4, 8 mg/kg/h 5-hour continuous administration[f] (b) 4 mg/kg/h 5-hour continuous administration in combination with propranolol	i.v.	≥1 mg/kg/h: Continuous, dose-dependent increase in heart rate Co-administration of propranolol: Suppression of heart rate increase, decreased MAP	4.2.1.3.9 (Reference data)
	Anesthetized German shepherd dogs (n = 4-5/sex/group)	Arterial blood pressure, vascular resistance, ventricular function, end-diastolic pressure, cardiac output, coronary blood flow, ECG	Continuous administration[g] at 0,[c] 1, 3, 10, 30 mg/kg/h	i.v.	≥3 mg/kg/h: Dose-dependent decrease in MAP and vascular resistance	4.2.1.3.10 (Reference data)
Respiratory system	SD rats (n = 10 males/group)	Respiratory rate	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.12
Renal system	SD rats (n = 8/group)	Renal functions (urine volume, sodium concentration, potassium concentration, pH)	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	10 mg/kg: Decreased pH	4.2.1.3.13
Gastrointestinal system	Isolated guinea pig ileal specimens (4 specimens)	Gastrointestinal smooth muscle contraction	0,[a] 10, 100, 1000 nmol/L	*In vitro*	No effect	4.2.1.3.15
	SD rats (n = 10 males/group)	Gastrointestinal transport Gastric emptying	Single dose of 0,[a] 1, 3, 10 mg/kg	i.v.	No effect	4.2.1.3.14

a Aseptic physiological saline
b Dimethyl sulfoxide (DMSO)
c Physiological saline
d Administration was started at the lowest dose with a ≥2-day withdrawal period between doses.
e A ≥2-day withdrawal period was given between doses.
f Conducted as a cross-over study with a washout period.
g The dose was increased in a step-wise manner. The initial dose (0 mg/kg/h) was administered continuously for 2 hours, while each of the subsequent 4 doses was administered continuously for 30 minutes.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effect of clazosentan on cerebrovascular spasm

The applicant's explanation about the pharmacological effect of clazosentan:

ET-1 is a vasoconstrictor peptide produced mainly in endothelial cells (*Nature*. 1988;332:411-5). ET-1 exerts its effects via ET_A and ET_B receptors. ET_A receptors are expressed mainly in vascular smooth muscle cells including cerebral arteries and ET_B receptors in endothelial cells (*J Cardiovasc Pharmacol.* 1995;26:S326-8, *J Cardiovasc Pharmacol*. 2007;50:621-8). Although the mechanism of the onset of cerebrovascular spasm after aSAH is unclear, clinical and nonclinical data suggest the involvement of increased ET-1 production and ET_A receptor-medicated cerebral vasoconstriction (*Blood Vessels*. 1989;26:249-53, *Life Sci*. 1993;52:825-34, etc.), and cerebrovascular spasm is related to the development and poor prognosis of cerebral infarction as well as to poor functional outcome (*Stroke.* 2011;42:919-23, *Nat Rev Neurol.* 2014;42:635-57). Thus, therapeutic intervention is required against the occurrence of cerebrovascular spasm after cerebral aneurysmal rupture.

In *in vitro* studies, clazosentan bound to ET_A receptor and inhibited (a) ET_A receptor-mediated inositol trisphosphate/calcium signaling pathway and (b) ET-1-induced vasoconstriction. Also, clazosentan showed an approximately 1,000-fold higher affinity to ET_A receptor than to ET_B receptor and, in studies of the inhibitory effect against ET-1 function, inhibited ET_A receptor-mediated function at lower concentrations. In *in vivo* studies, intravenously administered clazosentan inhibited the ET-1-mediated hypertensive activity in a dose-dependent manner in normal rats. In a canine model of SAH, clazosentan suppressed the basilar artery constriction in a dose-dependent manner. Also in a rabbit model of SAH, clazosentan suppressed basilar artery constriction. These findings suggest that clazosentan suppresses post-SAH cerebrovascular spasm. There are no data on the inhibitory effect of clazosentan against ET receptors of animals used in these nonclinical studies. However, species difference is unlikely to exist in the inhibitory effect of clazosentan against ET receptors or in its selectivity for ET receptors, because the percent homology of amino acid sequence of ET_A and ET_B receptors, respectively, is 93% and 89% between humans and rats, 95% and 97% between humans and dogs, and 96% and 91% between humans and rabbits[1)]

Based on the above, clazosentan is considered to exert its effect against post-aSAH cerebrovascular spasm by suppressing ET-1/ET_A receptor pathway-mediated vasoconstriction through competitive inhibition of ET-1 binding to ET_A receptor.

PMDA's view:

In *in vitro* studies and in the *in vivo* study using normal mice, clazosentan suppressed ET-1-induced vasoconstriction mediated by ET_A receptor. In *in vivo* studies using animal models of SAH, clazosentan suppressed post-SAH basilar artery constriction in a dose-dependent manner. Given the currently supposed mechanism of the onset of cerebrovascular spasm, the mechanism of clazosentan to suppress cerebrovascular spasm has been generally demonstrated, suggesting that clazosentan is effective in suppressing post-aSAH cerebrovascular spasm.

1) Amino acid sequences were obtained from UniProt and analyzed using a sequence analysis software GENEIOUS.

3.R.2 Safety pharmacology

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

In human ether a-go-go related gene (hERG)-transfected cells, clazosentan did not affect hERG potassium current up to the maximum dose of 300 μmol/L, which is more than 20,000 times the C_{ss} of unbound clazosentan (14 nmol/L) in humans who received a continuous intravenous administration of clazosentan 10 mg/h. A decrease in MAP was observed in rats, dogs, and minipigs that received clazosentan; the decrease was correlated with the decrease in the systemic vascular resistance, suggesting that it was due to the peripheral vasodilator action of clazosentan. In a telemetry study in dogs (CTD 4.2.1.3.9 and 4.2.1.3.11), clazosentan increased the heart rate in a dose-dependent manner. Propranolol suppressed the increased heart rate and caused a more marked decrease in MAP, suggesting that the clazosentan-induced heart rate increase was reflex tachycardia. No such reflex tachycardia was observed in minipigs (CTD 4.2.1.3.8). Since the MAP-lowering effect of clazosentan is considered to be due to vasodilatation mediated by the competitive effect on ET_A receptor, the MAP-lowering effect may pose a clinical problem in patients treated with clazosentan.

PMDA's view:

As for the effect of clazosentan on the cardiovascular system, clazosentan is unlikely to pose a clinical problem in hERG current, because hERG current was not affected by clazosentan at a sufficiently higher concentration than the concentration in humans receiving the clinical dose. On the other hand, a blood pressure decrease is expected from the pharmacological effect of clazosentan, and its safety in humans is discussed in Section "7.R.3.3 Adverse events related to hypotension."

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

Clazosentan concentration in plasma was measured by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) or high performance thin layer chromatography (HPTLC). The lower limit of quantitation of plasma clazosentan concentration was as follows:

LC-MS/MS: 50, 50, and 0.5 to 50 ng/mL, respectively, in rats, rabbits, and dogs

HPTLC: 100 to 1000 ng/mL by HPTLC in all of the rats, dogs, and minipigs

Pharmacokinetic (PK) parameters are expressed in mean or in mean ± SD unless specified otherwise. The dose of clazosentan sodium is expressed as the equivalent dose of clazosentan.

4.1 Absorption

4.1.1 Single-dose administration (CTD 4.2.2.2.1, and 4.2.2.3.1 to 4.2.2.3.3)

Clazosentan or ^{14}C-labeled clazosentan was administered intravenously as a single bolus or continuous infusion to male and female rats, male rabbits, male dogs, male minipigs, male cynomolgus monkeys, and female rhesus monkeys. Table 4 shows PK parameters of clazosentan observed.

Table 4. PK parameters of clazosentan after intravenous administration of clazosentan or ^{14}C-clazosentan

Animal species	Dose (mg/kg)	Infusion time	Sex	No. of animals	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg•h/mL)	$t_{1/2}$ (h)	t_{max}[a] (h)	CL (mL/min/kg)	V_{ss} (L/kg)
Rats	10	Bolus	Male	4	39.8 ± 2.5[b]	12.8 ± 1.0	0.8 ± 0.2	-	11.7 ± 2.0	0.32 ± 0.10
	60	6 h	Male	3	-	123 ± 18.8		-		
	24[c]	3 h	Male	2	8.89, 19.3[d]	26.7, 51.0[d]	4.75, 5.27[d]	2.00, 2.00[d]	7.85, 15.0[d]	0.45, 0.86
			Female	2	9.63, 14.6[d]	29.6, 42.4[d]	7.34, 13.8[d]	1.00, 2.00[d]	9.43, 13.5[d]	0.65, 1.80
Rabbits	10	Bolus	Male	3	26.8 ± 5.5[b]	6.05 ± 1.43	2.6 ± 0.6	-	26.8 ± 7.3	1.38 ± 0.09
Dogs	5	Bolus	Male	2	61.7, 76.1[b,d]	22.1, 38.8[d]	0.75, 1.11[d]	-	2.15, 3.77[d]	0.08, 0.10[d]
	24[c]	3 h	Male	3	46.3 ± 21.9	176 ± 91	9.7 ± 4.8	3.00	3.1 ± 2.2	0.45 ± 0.31
Minipigs	24[c]	3 h	Male	3	6.1 ± 1.2	16.93 ± 3.73	22.6 ± 3.9	2.00	23.6 ± 5.8	9.61 ± 2.04
Cynomolgus monkeys	10	Bolus	Male	2	37.8, 52.6[b,d]	8.88, 11.1[d]	0.54, 0.57[d]	-	15.1, 18.8[d]	0.16, 0.24[d]
Rhesus monkeys	10	Bolus	Female	3	35.9 ± 12.7[b]	8.63 ± 1.96	0.8 ± 0.2	-	19.0 ± 4.5	0.36 ± 0.26

a Median
b Plasma clazosentan concentration at 5 minutes after administration
c ^{14}C-labeled clazosentan was administered.
d Individual values in 2 animals are recorded.

4.1.2 Repeated-dose administration (CTD 4.2.3.2.2, 4.2.3.2.9, and 4.2.3.2.13)

Clazosentan was administered intravenously continuously for 28 days to male and female rats, male and female dogs, and male minipigs. Table 5 shows PK parameters observed.

Table 5. PK parameters of clazosentan after continuous intravenous administration of clazosentan

Animal species	Dose (mg/kg/day)	No. of animals	Measuring time point (Day)	Sex	C_{ss} (μg/mL)	AUC_{0-t} (μg•h/mL)
Rats	96	2	1[a]	Male	0.74, 1.05[d]	-
				Female	0.56, 1.17[d]	-
			28	Male	0.60, 1.92[d]	463, 899[d]
				Female	3.28, 8.48[d]	1050, 1810[d]
	384	2	1[a]	Male	7.89, 8.89[d]	-
				Female	7.54, 10.8[d]	-
			28	Male	11.0, 12.6[d]	7670, 9170[d]
				Female	5.85, 9.20[d]	5370, 5510[d]
Dogs	24	8	1[b]	Male	4.13 ± 1.26	-
				Female	3.42 ± 1.62	-
			28	Male	3.38 ± 0.75	-
				Female	4.33 ± 1.04	-
	96	8	1[b]	Male	25.1 ± 8.03	-
				Female	18.3 ± 5.91	-
			28	Male	17.0 ± 5.17	-
				Female	22.8 ± 6.36	-
Minipigs	96	3	1[c]	Male	1.70 ± 0.23	-
			28	Male	1.74 ± 0.63	-
	192	5	1[c]	Male	4.42 ± 1.13	-
			28	Male	3.26 ± 0.75	-

a Measured at 5 hours after the start of clazosentan administration.
b Measured at the end of administration on Day 1.
c Measured at 24 hours after the start of clazosentan administration.
d Individual values in 2 animals

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.2)

^{14}C-labeled clazosentan 24 mg/kg was administered intravenously continuously for 3 hours to male and female albino rats. Radioactivity concentration in each tissue at the end of administration, 0.5, 2, 12, 24, 72, 168, and 336 hours after administration was measured by whole-body autoradiography (n = 1/sex/time point). In most of the tissues and blood, the radioactivity concentration peaked between the end of administration and 2 hours after the end of administration. The highest radioactivity

concentrations observed in the following tissues were higher than that in blood (3.41 μg eq/L in males, 9.63 μg eq/L in females): Small intestine (498.5 μg eq/L, 401.3 μg eq/L), large intestine (454.1 μg eq/L, 368.4 μg eq/L), liver (11.00 μg eq/L, 14.86 μg eq/L), and kidney (7.43 μg eq/L, 8.19 μg eq/L). In both males and females, radioactivity concentrations in most of the tissues decreased to a level near or below the lower limit of quantitation within 24 hours after the end of administration, except those in the liver, kidney, lung, and gastrointestinal tract. At 72 hours after the end of administration, only the kidney had a quantifiable level of radioactivity.

^{14}C-labeled clazosentan 24 mg/kg was administered intravenously continuously for 3 hours to male and female pigmented rats. Radioactivity concentration in each tissue at the end of administration, 2, 24, and 72 hours after administration was measured by whole-body autoradiography (n = 1/sex/time point). The distribution of radioactivity in each tissue at each time point was generally similar to that observed in male and female albino rats above, with no accumulation of radioactivity in melanin-containing tissues (pigmented skin and eyes) observed.

4.2.2 Binding to plasma proteins (CTD 4.2.2.3.4)

Following the addition of ^{14}C-labeled clazosentan (0.425-46.3 μg/mL) to plasma samples of rats, rabbits, dogs, minipigs, cynomolgus monkeys, and rhesus monkeys, the fraction bound to plasma protein was found to be 99.56% to 99.65%, 98.61% to 98.91%, 93.92% to 95.84%, 93.45% to 94.13%, 96.91% to 97.29%, and 97.12% to 97.52%, respectively.

4.2.3 Distribution in blood cells (CTD 4.2.2.3.4 and 4.2.2.3.5)

^{14}C-labeled clazosentan (0.4-46 μg/mL) was added to blood samples of rats, rabbits, and dogs. The mixtures were incubated for 5 to 30 minutes at 36°C. The blood/plasma concentration ratio of clazosentan was 0.57 to 0.59 (rat), 0.65 to 0.66 (rabbit), and 0.55 (dog).

Following a single intravenous administration of ^{14}C-labeled clazosentan (10 mg/kg) to male rats, blood/plasma concentration ratio of the radioactivity at 0.25, 1, and 8 hours after the administration was 0.59 to 0.74 (n = 1/time point).

4.2.4 Placental transfer

The applicant's explanation:
No study of placental transfer of clazosentan was conducted. However, clazosentan is highly likely to be transferred to fetus via placenta, given the following findings: In the embryo-fetal toxicity studies in rats and rabbits, fetuses of female animals treated with clazosentan showed skeletal and visceral abnormalities as well as increased fetal motility.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4.1 to 4.2.2.4.3)

^{14}C-labeled clazosentan (5-50 μmol/L) was added to hepatic microsomes of rats, rabbits, dogs, and cynomolgus monkeys and to renal microsomes of rats. The mixtures were incubated for 1 hour at 37°C. M1 (metabolite generated by hydroxylation of 5-methyl group of pyridine sulfonamide in clazosentan) was the only metabolite formed by the hepatic microsomes of rats and rabbits, and no

metabolite was detected in the hepatic microsomes of dogs and monkeys or in the renal microsomes of rats.

^{14}C-labeled clazosentan 10 μmol/L was added to liver slices of dogs, and the mixture was incubated for 24 hours at 37°C. No metabolite was detected.

^{14}C-labeled clazosentan 3 or 10 μmol/L was added to liver cells of mice, rats, rabbits, dogs, minipigs, and cynomolgus monkeys. The mixtures were incubated for 48 or 72 hours at 37°C. Main metabolites detected were M1 and M4 (structure unidentified) in mice, M1 in rats, M6 (structure unidentified) in rabbits, and M1, M2 (structure unidentified), and M6 in minipigs. No metabolite was formed by dog or cynomolgus monkey liver cells.

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma, urine, feces, and bile (CTD 4.2.2.4.2 and 4.2.2.4.4)

Following a single intravenous administration of ^{14}C-labeled clazosentan 9.4 mg/kg to bile duct-cannulated male rats (n = 2), metabolites of clazosentan were hardly detected in the plasma up to 30 minutes after administration, in urine up to 8 hours after administration, and in bile up to 48 hours after administration (the rate of radioactivity of metabolites, expressed as a percentage of the administered radioactivity, was <2%).

A single dose of ^{14}C-labeled clazosentan 0.87 mg/kg was administered intravenously to bile duct-cannulated male dog (n = 1). No metabolites of clazosentan were detected either in plasma up to 6 hours after administration or in urine or bile up to 72 hours after administration.

Following a single intravenous administration of ^{14}C-labeled clazosentan 9.9 mg/kg to untreated male rats (n = 5), metabolites of clazosentan were not detected in urine up to 7 hours after administration, and only M1 was detected in urine from 7 to 24 hours after administration (the rate of radioactivity of M1, expressed as a percentage of the administered radioactivity, was ≤0.042%).

Following a single intravenous administration of ^{14}C-labeled clazosentan 0.87 mg/kg to untreated male dogs (n = 2), metabolites of clazosentan were hardly detected in urine and feces up to 72 hours after administration (the rate of radioactivity of metabolites, expressed as a percentage of the administered radioactivity, was 1.29% [urine] and 1.94% [feces]).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (CTD 4.2.2.3.1, 4.2.2.3.2, 4.2.2.5.1, and 4.2.2.5.2)

Following a single intravenous administration of ^{14}C-labeled clazosentan 9.9 mg/kg to male rats (n = 5), the excretion rate of radioactivity (expressed as a percentage of the administered radioactivity) up to 96 hours after administration was 14.73% in urine and 84.19% in feces.

Following a single intravenous administration of ^{14}C-labeled clazosentan 0.94 mg/kg to male dogs (n = 2), the excretion rate of radioactivity up to 96 hours after administration was 22.29% in urine and 71.08% in feces.

Following a continuous intravenous administration of ^{14}C-labeled clazosentan 24 mg/kg for 3 hours to bile duct-cannulated male and female rats (n = 3/sex), the urinary, fecal, and biliary excretion rate up to 72 hours after administration was 23.91%, 0.96%, and 74.61%, respectively, in males and 7.47%, 0.15%, and 91.95%, respectively, in females.

Following a continuous intravenous administration of ^{14}C-labeled clazosentan 24 mg/kg for 3 hours to bile duct-cannulated male dogs (n = 3), the urinary, fecal, and biliary excretion rate up to 72 hours after administration was 25.47%, 0.96%, and 68.38%, respectively.

4.4.2 Excretion in milk

The applicant's explanation:

No study was conducted on clazosentan excretion in milk. However, since clazosentan is a substrate for breast cancer resistance protein (BCRP), it is expected to be transferred from blood to milk by active transport mediated by BCRP.

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 nonclinical pharmacokinetics of clazosentan was evaluated appropriately.

4.R.1 Tissue distribution

PMDA asked the applicant to explain whether safety problems arise in humans from the distribution of clazosentan or its metabolites in the liver, kidney, and gastrointestinal tract, the organs that showed extensive accumulation of radioactivity in the tissue distribution studies [see Section "4.2.1 Tissue distribution"].

The applicant's explanation:

Distribution of clazosentan or its metabolites in the liver, kidney, or gastrointestinal tract is unlikely to pose a safety problem, judging from the results of the following toxicological studies.

(a) Effect on the liver

A maximum tolerated dose (MTD) study in dogs[2)] showed the following histopathological changes in the liver in some of the treatment groups: Hemosiderin deposition, increased erythrophagia in Kupffer cells, and diffuse microgranuloma. These findings were within the range of the historical pathological findings in normal beagle dogs, and their causal relationship to clazosentan was unclear. In a 2-week continuous intravenous dose toxicity study in dogs,[3)] hyaline droplets were observed in liver cells of animals in all clazosentan groups, but were found to have been reversed at the end of the 16-week withdrawal period, except in 1 animal in the 96 mg/kg group. Hyaline droplets in liver cells of the

2) Clazosentan was administered to male and female beagle dogs (n = 2/sex) intravenously continuously for 1 day at each dose of 48, 96, 192, and 384 mg/kg in this order and, after a 5-day withdrawal period, clazosentan was administered intravenously continuously for 5 days at a dose of 384 mg/kg/day.

3) Clazosentan 0 (0.9% sodium chloride solution), 6, 24, and 96 mg/kg/day was administered to male beagle dogs (n = 3/group) intravenously continuously for 2 weeks. After the end of the administration period, animals were subjected to a 16-week withdrawal period to evaluate reversibility.

animal in the 96 mg/kg group were within the range of the historical pathological findings in normal beagle dogs; therefore they were incidental findings unrelated to clazosentan.

These findings were observed at the doses of 384 mg/kg (MTD study) and 96 mg/kg (2-week continuous intravenous dose toxicity study). C_{ss} of clazosentan was 155000 ng/mL at 384 mg/kg and 11790 ng/mL at 96 mg/kg. These C_{ss} levels in the MTD study and in the 2-week intravenous continuous dose toxicity study were approximately 460 and 36 times, respectively, the C_{ss} (331.4 ng/mL) in humans receiving intravenous continuous administration of clazosentan at 10 mg/h. No hepatic toxicity findings were observed in another continuous dose toxicity study up to 4 weeks in dogs or in the toxicity studies in rats and minipigs.

The above results collectively suggest that the liver is not the toxic target organ of clazosentan at the clinical dose.

(b) Effect on the kidney
No renal toxicity findings were observed in toxicity studies.

(c) Effect on the gastrointestinal tract
In continuous infusion toxicity studies in rats, dogs, and minipigs, brick red feces were observed in animals receiving medium to high doses (≥192 mg/kg/day in rats, ≥24 mg/kg/day in dogs, ≥96 mg/kg/day in minipigs). However, the findings were not considered to be toxic changes, because (a) occult blood test was negative, and (b) results of an *ex vivo* study suggest that the reddening of the feces are due to chelate formation of clazosentan with ferric ion in feces.

PMDA's view:
Given the low incidences of toxicity findings in tissues showing high radioactivity accumulation, the applicant's explanation (i.e., distribution of clazosentan or its metabolites in tissues showing high radioactivity accumulation is unlikely to pose a safety problem in humans) is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of repeated-dose toxicity studies, reproductive and developmental toxicity studies, genotoxicity studies, phototoxicity studies, hemolysis studies, and local tolerance studies.

In this section, the dose of clazosentan sodium is expressed as the equivalent dose of clazosentan.

5.1 Single-dose toxicity

No single-dose toxicity study was conducted. Instead, acute toxicity was evaluated in repeated intravenous dose toxicity studies in rats, dogs, and minipigs (CTD 4.2.3.2.2, 4.2.3.2.6, 4.2.3.2.7, 4.2.3.2.9, 4.2.3.2.11, and 4.2.3.2.12). No acute toxicity was observed up to the highest dose tested in any of the studies, with the approximate lethal dose determined to be >384 mg/kg in rats, >96 mg/kg in dogs, and >192 mg/kg in minipigs.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies up to 4 weeks were conducted in rats, dogs, and minipigs. Clazosentan was administered intravenously continuously in all studies (Table 6). Dogs and minipigs showed effects on the cardiovascular system caused by hemodynamic changes due to the pharmacological effect of clazosentan. This effect of clazosentan in dogs was detected from the lowest dose; therefore no observed effect level (NOEL) could not be determined in dogs. In the repeated-dose toxicity studies in rats and minipigs, C_{ss} of clazosentan at the NOEL (96 mg/kg/day in rats, 0.096 mg/kg/day in minipigs) was 1635 and 1.57 ng/mL, respectively, which were approximately 5 times (rats) and approximately 0.005 times (minipigs) the C_{ss} (331.4 ng/mL) in humans receiving continuous intravenous administration of clazosentan 10 mg/h.

Table 6. Repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	i.v.	4 weeks + 4-week withdrawal	0,[a] 96, 192, 384	≥192: Seminiferous tubules expanded Reversible	96	4.2.3.2.2
Male dogs (beagle)		2 weeks + 16-week withdrawal	0,[b] 6, 24, 96	≥6: Heart rate increased; arteritis (extramural/intramural intimal thickening, medial degeneration/necrosis, growth of outer membrane of coronary arteries); cardiomyocyte degeneration, necrosis, and fibrosis of right atrium; interstitial edema of pericardial fat; expansion, vacuolization, and atrophy of seminiferous tubules ≥24: Increased right coronary artery diameter; thickness and dark reddening of left auricle; endocardial hyperplasia; epicardial inflammation and fibrosis; atrial vascular growth; inflammation foci in pericardial fat; biliary hypersecretion[c] Reversible	<6	4.2.3.2.6 4.2.3.2.7
Male and female dogs (beagle)		4 weeks + 4-week withdrawal	0,[b] 24, 96	≥24: Right atrial cardiac fibrosis, arteritis Reversible: (except cardiac fibrosis and arteritis in the 96 mg/kg/day group)	<24	4.2.3.2.9
Male and female minipigs (Göttingen)		2 weeks + 16-week withdrawal	0,[a] 0.096, 9.6, 96	≥0: Degeneration and atrophy of seminiferous tubules ≥9.6: Polyarthritis and periarteritis (intestinal tract, kidney, stomach, testis, ovary, spleen, trachea, etc.), seminiferous tubule dilatation Reversible	0.096	4.2.3.2.11
Male minipigs (Göttingen)		4 weeks + 10-week withdrawal	0,[b] 96, 192	≥0: Degeneration and atrophy of seminiferous tubule ≥96: Polyarthritis, arterial fibrinoid necrosis, seminiferous tubule dilatation Reversible	<96	4.2.3.2.12

a Tris-buffered physiological saline (pH 8.0)
b 0.9% sodium chloride solution
c The applicant determined that clazosentan is unlikely to pose safety concerns in clinical use because biliary hypersecretion was observed only in dogs receiving more than a 10-times higher dose of clazosentan than the exposure in humans, and were completely reversible after the withdrawal period.

5.3 Genotoxicity

The following genotoxicity studies of clazosentan were conducted: *In vitro* studies (bacterial reverse mutation assay, a chromosomal aberration assay using cultured human lymphocytes, and murine lymphoma TK study) and an *in vivo* micronucleus assay with mouse myeloma cells. No genotoxicity was demonstrated (Table 7).

Table 7. Genotoxicity studies

Study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg)	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium:* TA97, TA98, TA100, TA1535, TA1537, TA102 *Escherichia coli:* WP2*uvrA*	S9 –/+	0,[a] 50, 166, 500, 1666, 5000	Negative	4.2.3.3.1.1
	Chromosomal aberration assay	Cultured human peripheral lymphocytes	S9 – (21 hours)	0,[b] 500, 2000, 3500	Negative	4.2.3.3.1.2
			S9 + (3 hours)	0,[b] 500, 1000, 2000, 3500	Negative	
	Mouse lymphoma TK assay	Cultured mouse lymphoma cells L5178Y $TK^{+/-}$	S9 –/+ (3 hours)	0,[a] 78.13 to 5000	Negative	4.2.3.3.1.3
In vivo	Micronucleus assay in rodents	Mouse (Füllinsdorf Moro Albino) bone marrow		0,[c] 250, 500, 1000	Negative	4.2.3.3.2.1

a Water
b DMSO
c Tris (hydroxymethyl)-aminomethane, SEQUESTREN Na_2, NaCl, HCl 0.1 N ad pH 8.0

5.4 Carcinogenicity

Since clazosentan is used for only a brief period in humans, no carcinogenicity study was conducted on clazosentan.

5.5 Reproductive and developmental toxicity

The following studies were conducted: Studies on fertility in male and female rats, a study on embryo-fetal development in rats, a study on embryo-fetal development in rabbits, and a study on effects on pre- and postnatal development, including maternal function in rats. Clazosentan was administered intravenously continuously in all of these studies (Table 8). Skeletal and visceral anomalies in fetuses were observed in all clazosentan groups of all studies. These findings are common to all ERAs, and the applicant determined that clazosentan should be contraindicated in pregnant women.

Table 8. Reproductive toxicity studies

Study	Test system	Route of admini-stration	Treatment duration	Dose (mg/kg/day)	Main findings	No observed adverse effect level (mg/kg/day)	Attached document CTD
Studies on fertility in male rats	Male rats (SD)	i.v.	8 weeks before mating to the end of mating (13 weeks in total)	0,[a] 96, 192, 384	*Parental animals* ≥96: Reduction in body weight gain, atrophy of seminiferous tubules, increased testis weight *Fertility* None	*Parental animals* General toxicity: 384 *Fertility* 384	4.2.3.5.1.1
Composite study on fertility and embryo-fetal development	Female rats (SD)		2 weeks before mating to Gestation Day 7 (Caesarean section on Gestation Day 13)		*Parental animals* None *Fertility* None *Embryos/fetuses* None	*Parental animals* General toxicity: 384 *Fertility* 384 *Embryos/fetuses* 384	4.2.3.5.1.2
Study on embryo-fetal development	Female rats (SD)		Gestation Day 6 to 17 (Caesarean section on Gestation Day 20)		*Parental animals* 384: Increased post-implantation loss *Fetuses* ≥96: Delayed ossification, decreased mean fetal weight, mandibular defects, major defects of the thoracic blood vessels (aortic arch among others) ≥192: Systemic edema, malformation of thyroid gland, dwarf thymus 384: Decreased live fetal count	*Parental animals* General toxicity: 192 *Embryos/fetuses* <96	4.2.3.5.2.1
	Female rabbits (NZW)		Gestation Day 6 to 19 (Caesarean section on Gestation Day 29)	0,[a] 24, 72, 204	*Maternal animals* ≥24: Decreased food consumption/body weight ≥72: Increased early resorptions/postimplantation loss *Fetuses* ≥24: Dilatation of aortic arch, dilatation of pulmonary arterial arch, persistent truncus arteriosus, enlarged ventricular cavity 204: Decreased live fetal count	*Parental animals* General toxicity: <24 *Embryos/fetuses* <24	4.2.3.5.2.3
Study on effects on pre- and postnatal development, including maternal function	Rats (SD)		Postmating Day 17 to Postpartum Lactation Day 20	0,[a] 96, 192, 384	*Maternal animals* Death[b] ≥96: Increased postimplantation loss *F1 offspring* 384: Decreased suckling power, delayed testicular descent, decreased locomotor activity, decreased mating success rate	*Parental animals* <96 *F1 offspring* 192	4.2.3.5.3.1

a Tris-buffered saline (pH 8.0)

b Death related to administration technique (4 animals in the 0 mg/kg/day group, 9 animals in the 96 mg/kg/day group, 13 animals in the 192 mg/kg/day group, 13 animals in the 384 mg/kg/day group

5.6 Local tolerance (CTD 4.2.3.6.1 to 4.2.3.6.3)

Intravenous local tolerance studies were conducted in rats, rabbits, and dogs. There were no findings of any concern under the clinical dosing conditions.

5.7 Other studies

5.7.1 Hemolysis (CTD 4.2.3.7.7.1)

Hemolysis studies were conducted using whole blood and plasma of dogs. No hemolytic activity was observed up to the maximum concentration tested (25 mg/mL).

5.7.2 Phototoxicity (CTD 4.2.3.7.7.2)

Phototoxicity of clazosentan against BALB/c 3T3 fibroblasts was investigated by neutral red uptake assay. The phototoxicity of clazosentan up to 100 μg/mL was evaluated with or without ultraviolet A irradiation. Results showed no phototoxicity.

5.7.3 Safety of impurities

All impurities described in the proposed specifications of clazosentan drug substance were present in the drug substance used in the toxicity studies in amounts exceeding the exposure expected in humans. This allowed safety evaluation based on data from the toxicity studies. The drug product did not contain impurities in amounts exceeding the threshold level specified by the ICH Q3B Guidelines.

5.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 nonclinical toxicity studies showed no findings suggestive of problems in clinical use of clazosentan.

5.R.1 Effect on cardiovascular system

The applicant's explanation about the effect on the cardiovascular system observed in the repeated-dose toxicity studies on dogs and minipigs (Table 6):

The cardiovascular system of dogs is prone to be affected by changes in hemodynamics, and administration of ERA for a short period causes inflammation in the coronary arteries (*Toxicol Pathol.* 2001;29:277-84, *Toxicol Pathol*. 2003;31:263-72, etc.). The inflammation is induced by the following mechanism: Persistent dilatation of blood vessels in the coronary vascular bed causes changes in hemodynamics, leading to increased shear stress and tension of the coronary artery wall and damage of internal elastic lamina (*Toxicol Pathol*. 2003;31:263-72). The toxicity profile of the cardiovascular system observed in dogs after clazosentan administration was similar to the findings known to occur after ERA administration. In minipigs, arteritis occurs spontaneously (*Toxicol Pathol.* 2018;46:121-30, The minipig. In: *Animal models in toxicology.* 2nd ed. CRC Press; 2006:731-71, etc.). In the toxicity study of clazosentan in minipigs, myocarditis was not observed but arteritis was observed in the control group as well as in the clazosentan group (CTD 4.2.3.2.12). The histology of arteritis in the control group was similar to that in the clazosentan group; this suggests that the arteritis observed in the clazosentan group was an aggravated condition of historical findings commonly observed in minipigs and the aggravation was caused by clazosentan-induced hemodynamics change. No similar findings were observed in rats. Vascular lesions in experimental animals caused by small molecule drugs are not generally related to vascular injuries in humans (*Toxicol Pathol*. 2014;42:658-71, *Crit*

Rev Toxicol. 1992;22:203-41, etc.), suggesting that the above findings observed in animals are unlikely to be related to humans. In addition, these findings observed in dogs and minipigs showed a tendency of reversibility, except in some dogs that received clazosentan at a high dose (96 mg/kg/day), which resulted in approximately 60 times higher C_{ss} than that (331.4 ng/mL) in humans receiving continuous intravenous administration of 10 mg/h (CTD 4.2.3.2.9). This shows that clazosentan is unlikely to pose any safety problems in clinical use.

PMDA's view:
Taking account of the applicant's explanation, the effect of clazosentan on the cardiovascular system observed in dogs and minipigs is unlikely to pose a safety risk in humans in clinical use.

5.R.2 Effect on testis

PMDA asked the applicant to explain whether the testicular findings observed in rats, dogs, and minipigs (seminiferous tubule dilatation, degeneration/atrophy of seminiferous tubules) pose safety concerns in humans receiving clazosentan.

The applicant's explanation:
Seminiferous tubule dilatation is caused by the pharmacological effect of clazosentan on smooth muscle cells around the seminiferous tubules. It is a known effect common to ERA. It is known that the seminiferous tubule dilatation caused by drugs of the same class is recovered completely after withdrawal and does not affect the sperm parameters of patients. In a similar manner, the seminiferous tubule dilatation observed in rats, dogs, and minipigs after clazosentan administration was reversible after a withdrawal period. Also, no abnormality was observed in the sperm test (morphology, motility) in the repeated-dose toxicity studies in dogs and minipigs or in the fertility test in rats. Degeneration/atrophy of seminiferous tubules are degenerative changes caused by the compression of the seminiferous epithelia as a result of retention of seminiferous tubule fluid in the seminiferous tubule lumen due to ERA-induced persistent seminiferous tubule dilatation. These findings were observed with similar drugs after a long-term administration in toxicity studies. The repeated-dose toxicity studies of clazosentan in dogs and minipigs were conducted for only up to 4 weeks, and probably the study duration was insufficient to cause these degenerative changes. Dogs and minipigs are known to have spontaneous atrophy of seminiferous tubules at a high rate (87% in dogs, 70% in minipigs) (*Interpretation and Relevance in Drug Safety Evaluation.* 4th ed. Elsevier; 2012:298-300, *Toxicol Pathol.* 2000;28:782-7, etc.). Degeneration/atrophy of seminiferous tubules observed in dogs and minipigs after clazosentan administration was also observed in the control groups of both animal species, and neither their incidences nor the severity of the findings was correlated with the dose of clazosentan; the applicant therefore determined that the testicular findings were accidental historical events that were detected.

Thus, the only testicular findings related to clazosentan is seminiferous tubule dilatation which is a reversible change based on the action mechanism common to ERA. Clazosentan is therefore unlikely to pose any safety problems because clazosentan is used only in a short period clinically.

PMDA's view:

There is a certain reasonableness in the applicant's explanation that the 4-week toxicity studies of clazosentan was not long enough to induce degenerative changes of the testis. The submitted toxicity data do not clearly suggest clazosentan-induced degenerative changes of the testis. However, seminiferous tubule dilatation and accompanying degenerative changes (necrosis/atrophy of seminiferous tubules) are findings expected from the pharmacological effect of clazosentan, and irreversible effects on the testis were observed in toxicity studies of other ERAs. Accordingly, the possibility cannot be excluded that clazosentan may have some effect on human testis. The testicular findings observed in the toxicity studies should be described in the package insert to provide information.

5.R.3 Effect on fetuses

Effects on fetuses, which are known and common to ERAs, were observed in the embryo-fetal development toxicity studies of clazosentan. The applicant's proposal to contraindicate clazosentan in pregnant women is appropriate, as described in Section "5.5 Reproductive and developmental toxicity."

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

PK parameters are expressed in mean or in mean ± SD unless specified otherwise. In this section, the dose of clazosentan sodium is expressed as the equivalent dose of clazosentan.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma clazosentan concentration was measured by LC-MS/MS. The lower limit quantitation of the plasma concentration was 0.250 to 4 ng/mL.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.4)

Following the addition of ^{14}C-labeled clazosentan (0.142-42.4 ng/mL) to human plasma, the plasma protein bound fraction was 97.32% to 97.74%.

^{14}C-labeled clazosentan (0.4-46 µg/mL) was added to human blood, and the mixture was incubated for 5 to 30 minutes at 36°C. The blood/plasma concentration ratio of clazosentan was 0.58 to 0.59.

6.2.1.2 *In vitro* metabolism

6.2.1.2.1 Metabolism of clazosentan (CTD 4.2.2.4.1 to 4.2.2.4.3)

^{14}C-labeled clazosentan 12.5 µmol/L was added to human liver microsomes, and the mixture was incubated for 1 hour at 37°C. The only metabolite detected was M1, which accounted for 6% of the total radioactivity added.

^{14}C-labeled clazosentan 10 μmol/L was added to human liver slices, and the mixture was incubated for 24 hours at 37°C. The main metabolite detected was M1, which accounted for 2.3% of the total radioactivity added.

^{14}C-labeled clazosentan 10 μmol/L was added to human liver cells, and the mixture was incubated for 24, 48, and 72 hours at 37°C. The main metabolite detected was M1, which accounted for 28% (24 hours), 53% to 77% (48 hours), and 65% (72 hours) of the total radioactivity.

6.2.1.2.2 Studies of enzymes involved in the metabolism of clazosentan (CTD 4.2.2.4.5)

^{14}C-labeled clazosentan 10 μmol/L was added to microsomes expressing recombinant human cytochrome P450 (CYP)1A2, CYP2C9, CYP2D6, or CYP3A4. The mixtures were incubated for 1 hour at 37°C. M1 was detected only in the presence of CYP2C9, and accounted for 19% of the total radioactivity in the sample.

^{14}C-labeled clazosentan 10 μmol/L was added to human liver microsomes. The mixture was incubated for 1 hour at 37°C in the presence or absence of a specific inhibitor of CYP3A4 (midazolam, 64 μmol/L) or a specific inhibitor of CYP2C9 (sulfaphenazole, 50 μmol/L). Metabolism to M1 was inhibited only in the presence of the specific inhibitor of CYP2C9. The M1 concentration in the presence of the inhibitor of CYP2C9 was 15% of the M1 concentration in the absence of the inhibitor.

6.2.1.3 Inhibition of CYP isoforms (CTD 4.2.2.6.1 and 4.2.2.6.2)

Using human liver microsomes, recombinant human CYP2B6 or CYP2C19, and substrates of respective CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), the inhibitory effect of clazosentan (0.1-50 μmol/L) against each CYP isoform was investigated (0.1-200, 0.1-100, and 0.1-100 μmol/L, respectively, in the study on CYP2A6, CYP2C8, and CYP2E1). Clazosentan inhibited CYP2C8 with IC_{50} of 43 μmol/L. Clazosentan showed little inhibitory effect against other CYP isoforms (IC_{50} exceeded the maximum concentration tested). The inhibitory effect of clazosentan against CYP2C8 was not time-dependent.

6.2.1.4 Enzyme induction (CTD 4.2.2.6.3 and 4.2.2.6.4)

Human liver cells were incubated with clazosentan (0.3-30 μmol/L) for 48 to 72 hours at 37°C to investigate the induction of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 by clazosentan. Clazosentan hardly induced messenger ribonucleic acid (mRNA) expression or enzyme activity of any of the CYP isoforms investigated.

6.2.1.5 Studies on transporters

6.2.1.5.1 Madin-Darby canine kidney strain II (MDCKII) cell permeability (CTD 4.2.2.6.7)

Following the addition of ^{14}C-labeled clazosentan (1-100 μmol/L) to MDCKII cells, the apparent apical-to-basal permeability coefficient (P_{app} A→B) of clazosentan was 0.1 to 0.4 $\times 10^{-6}$ cm/s and the apparent basal-to-apical permeability coefficient (P_{app} B→A) was 0.1 to 0.2 $\times 10^{-6}$ cm/s. The efflux ratio was 0.4 to 1.6.

6.2.1.5.2 Transporter-mediated clazosentan transport (CTD 4.2.2.6.5 and 4.2.2.6.7)

^{14}C-labeled clazosentan (0.375-7.5 μmol/L) was added to membrane vesicles prepared from P-glycoprotein (P-gp)-expressing human cells in the presence of adenosine triphosphate (ATP) or adenosine monophosphate (AMP). The extent of the intracellular uptake of clazosentan in the presence of ATP was similar to that observed in the presence of AMP.

^{14}C-labeled clazosentan 1 μmol/L was added to membrane vesicles prepared from Sf9 cells engineered to express BCRP in the presence of ATP or AMP, and this trial was repeated again (2 trials in total). The ratio of clazosentan uptake in the presence of ATP to that in the presence of AMP was 4.8 (first trial) and 4.3 (second trial). In the presence of a BCRP inhibitor (Ko143, 2 μmol/L), the ratio decreased to 3.7 (first trial) and 1.1 (second trial).

^{14}C-labeled clazosentan (0.075-7.5 μmol/L) was added to membrane vesicles prepared from HEK cells engineered to express multidrug resistance-associated protein (MRP)2 or bile salt export pump (BSEP) in the presence of ATP or AMP. The intracellular uptake of clazosentan in the presence of ATP was similar to that in the presence of AMP.

^{14}C-labeled clazosentan (0.05-75 μmol/L) was added to Chinese hamster ovary (CHO) cells engineered to express organic anion transporting polypeptide (OATP)1B1. Michaelis-Menten constant (K_m) of clazosentan to OATP1B1 was 5.9 ± 2.2 μmol/L. The uptake of clazosentan (3 μmol/L) into OATP1B1-expressing cells was 2.5 times the uptake into OATP1B1-nonexpressing cells.

^{14}C-labeled clazosentan (0.5-220 μmol/L) was added to CHO cells engineered to express OATP1B3. K_m of clazosentan to OATP1B3 was 6.0 ± 2.4 μmol/L. The uptake of clazosentan (3 μmol/L) into OATP1B3-expressing cells was 9.6 times the uptake into OATP1B3-nonexpressing cells.

6.2.1.5.3 Inhibitory effect of transporters (CTD 4.2.2.6.5, 4.2.2.6.6, and 4.2.2.6.8)

The inhibitory effect of clazosentan against transporters was investigated using membrane vesicles prepared from BCRP-, MRP2-, or BSEP-expressing cells or cells engineered to express P-gp, multidrug and toxic compound extrusion (MATE)1, MATE2-K, OATP1B1, OATP1B3, OATP2B1, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, or OCT2, and substrates for respective transporters.[4)] Table 9 shows the results.

4) Compounds used as substrates for transporters: Digoxin and colchicine for P-gp; methotrexate for BCRP; estradiol 17β-D-glucuronide for MRP2; taurocholic acid for BSEP; atorvastatin for OATP1B1; taurocholic acid for OATP1B3; estrone-3-sulfate for OATP2B1; para-aminohippuric acid for OAT1; estrone-3-sulfate for OAT3; 1-methyl-4-phenylpyridinium iodide for OCT1; 1-methyl-4-phenylpyridinium iodide for OCT2.

Table 9. Inhibitory effect of clazosentan against transporters

Transporter	Concentration (μmol/L)	IC_{50} (μmol/L)
P-gp	0.1-1000	>1000
BCRP	0.1-1000	92 ± 17
MRP2	0.1-1000	5.9 ± 0.7
BSEP	0.1-1000	123 ± 39
MATE1	0.01-100	>100
MATE2-K	0.01-100	>100
OATP1B1	0.5-600,[a] 0.1-100[b]	20 ± 2.9,[a] 33 ± 6[b]
OATP1B3	0.1-500,[a] 0.1-100[b]	8.4 ± 1.4,[a] 15 ± 6[b]
OATP2B1	0.05-500	6.5 ± 0.7
OAT1	0.1-1000	4.7 ± 1.0
OAT3	0.1-1000	4.6 ± 1.8
OCT1	0.01-100	>100
OCT2	0.1-1000	>1000

a Without preincubation
b Preincubated for 30 minutes

6.2.2 Studies in healthy adults

6.2.2.1 Dose escalation, continuous administration study in healthy Japanese and Caucasian adults (Study AC-054-101; CTD 5.3.3.3.3; Study period, [redacted] to [redacted] 20[redacted])

Clazosentan was administered intravenously to healthy Japanese and Caucasian adults continuously for 4 hours at the speed of 1 mg/h, for 4 hours at the speed of 5 mg/h, then for 4 hours at the speed of 15 mg/h. Table 10 shows PK parameters of clazosentan.

Table 10. PK parameters of clazosentan in continuous intravenous administration

Subjects	n	C_{max}[a] (ng/mL)	AUC_{0-4h} (ng•h/mL)	AUC_{4-8h} (ng•h/mL)	AUC_{8-12h} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
Japanese	12	421.50 ± 110.99	115 [104, 128]	580 [528, 638]	1507 [1345, 1689]	2366 [2133, 2623]	2.4 [2.2, 2.6]	35.5 [32.0, 39.4]	9.9 [7.5, 13.0]
Caucasians	12	385.42 ± 81.35	92.3 [80.3, 106]	457 [392, 533]	1358 [1200, 1538]	2038 [1802, 2304]	2.6 [2.3, 2.9]	41.2 [36.5, 46.6]	15.5 [11.4, 21.0]

Geometric mean [95% CI]
a Time point of the maximum mean plasma clazosentan concentration, arithmetic mean ± SD

6.2.2.2 Continuous administration study in healthy non-Japanese adults (Study VML 588-1001; CTD 5.3.3.1.1 [Reference data]; Study period, [redacted] to [redacted])

Clazosentan was administered intravenously to healthy adult non-Japanese men continuously for 3, 6, or 12 hours at the speed of 3, 10, 30, or 60 mg/h. Table 11 shows PK parameters of clazosentan.

Table 11. PK parameters of clazosentan in continuous intravenous administration

Infusion speed (mg/h)	Duration of infusion (h)	n	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
3	3	6	73.49 ± 9.74	225.4 ± 29.68	0.908 ± 0.13	40.53 ± 5.43	16.06 ± 2.47
10	3	6	252.6 ± 36.36	778.1 ± 113.8	0.971 ± 0.11	39.15 ± 4.90	17.38 ± 2.05
30	3	6	913.7 ± 85.14	2830 ± 282.3	0.725 ± 0.33	32.08 ± 3.35	15.17 ± 1.67
60	3	6	1541 ± 295.8	4728 ± 934.9	0.791 ± 0.37	39.27 ± 7.36	15.59 ± 4.11
60	6	6	1637 ± 280.1	9922 ± 1720	0.838 ± 0.41	37.19 ± 6.30	14.62 ± 2.02
30	12	3	686.4 ± 37.04	8239 ± 447.0	0.837 ± 0.52	43.78 ± 2.44	15.45 ± 3.08

6.2.2.3 Mass balance study (Study VML 588-1006; CTD 5.3.3.1.3 [Reference data]; Study period, [redacted] to [redacted])

^{14}C-labeled clazosentan was administered intravenously to 4 healthy adult non-Japanese men continuously for 3 hours at the speed of 0.2 mg/kg/h. The excretion rate of radioactivity (percentage of

the administered radioactivity) up to 192 hours after administration was 15.0% ± 3.5% in urine and 80.9% ± 3.0% in feces. Clazosentan accounted for up to 93.4% of the radioactivity in plasma, and there was no radioactive peak other than that of clazosentan in plasma. Most of the radioactivity excreted in urine and feces was clazosentan, and excreted metabolites accounted for ≤5% of total administered radioactivity.

6.2.3 Study in patients

6.2.3.1 Japanese and South Korean joint phase II study (Study AC-054-202; CTD 5.3.5.1.3; Study period, [redacted] to [redacted])

Japanese and South Korean patients who had undergone clipping for aSAH received continuous intravenous administration of clazosentan at the speed of 5 or 10 mg/h until Day 14 after aSAH onset. Table 12 shows plasma clazosentan concentration on Days 7 to 11 after aSAH onset.

Table 12. Plasma clazosentan concentration in continuous intravenous administration of clazosentan

Subjects	Dose (mg/h)	n	Plasma clazosentan concentration (ng/mL)
Japanese	5	30	148.2 (48.64)
	10	33	317.0 (75.55)
South Korean	5	25	183.6 (118.73)
	10	23	353.4 (141.33)

Geometric mean (coefficient of variance, %)

6.2.4 Studies of intrinsic factors

6.2.4.1 Clinical pharmacology study in patients with hepatic impairment (Study AC-054-104; CTD 5.3.3.3.2; Study period, [redacted] to [redacted])

Clazosentan was administered intravenously continuously for 6 hours at the speed of 0.5 or 1.0 mg/h to non-Japanese subjects in the following groups (n = 8/group):

(a) Subjects with mild hepatic impairment (Child-Pugh class A)
(b) Subjects with moderate hepatic impairment (Child-Pugh class B)
(c) Subjects with severe hepatic impairment (Child-Pugh class C)
(d) Subjects with normal hepatic function matched for baseline characteristics (age, body mass index [BMI], and sex) to the subjects with hepatic impairment

Table 13 shows PK parameters of clazosentan. The geometric mean ratio [90% confidence interval (CI)] of C_{ss} and $AUC_{0-\infty}$ of clazosentan (hepatic impairment/normal hepatic function) was 1.35 [1.02, 1.79] and 1.41 [1.04, 1.90], respectively, in subjects with mild hepatic impairment, 2.10 [1.59, 2.78] and 2.37 [1.75, 3.19], respectively, in subjects with moderate hepatic impairment, and 3.20 [2.42, 4.23] and 3.79 [2.81, 5.11], respectively, in subjects with severe hepatic impairment.

Table 13. PK parameters in continuous intravenous administration of clazosentan

Hepatic function of subjects	Infusion speed (mg/h)	n	C_{ss} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)	f_u (%)
Normal hepatic function	1.0	8	30.4 [24.8, 37.3]	174 [144, 211]	2.0 [1.5, 2.6]	34.5 [28.4, 41.9]	19.6 [15.3, 25.2]	2.2 [1.7, 2.7]
Mild hepatic impairment	1.0	8	41.1 [29.3, 57.6]	245 [169, 356]	2.9 [1.7, 5.1]	24.5 [16.8, 35.5]	22.4 [15.7, 31.8]	2.2 [1.8, 2.7]
Moderate hepatic impairment	1.0	8	63.8 [52.5, 77.5]	412 [331, 513]	4.9 [3.4, 6.9]	14.5 [11.7, 18.1]	22.4 [18.8, 26.6]	3.5 [2.9, 4.2]
Severe hepatic impairment	0.5	8	48.6 [34.9, 67.6]	330 [232, 469]	14.7 [7.4, 29.1]	9.1 [6.4, 12.9]	28.3 [20.3, 39.5]	4.9 [3.8, 6.3]

Geometric mean [95% CI]

6.2.4.2 Clinical pharmacology study in subjects with renal impairment (Study AC-054-103; CTD 5.3.3.3.1; Study period, [redacted] to [redacted] 20[redacted])

Clazosentan was administered intravenously continuously for 6 hours at the speed of 1 mg/h to non-Japanese subjects in the following groups (n= 8/group):

(a) Subjects with severe renal impairment (creatinine clearance [CL_{cr}] <30 mL/min)

(b) Subjects with normal renal function (CL_{cr} >80 mL/min) matched for baseline characteristics (age, BMI, and sex) to the subjects with renal impairment

Table 14 shows PK parameters of clazosentan in these subject groups. The geometric mean ratio [90% CI] of C_{ss} and $AUC_{0-\infty}$ of clazosentan (severe renal impairment/normal renal function) was 1.08 [0.89, 1.29] and 1.08 [0.91, 1.29], respectively.

Table 14. PK parameters of clazosentan in continuous intravenous administration of clazosentan

Renal function of subjects	n	C_{ss} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)	f_u (%)
Normal renal function	8	29.5 [26.1, 33.4]	169 [151, 190]	2.4 [1.9, 3.1]	35.5 [31.6, 39.8]	24.1 [23.0, 25.3]	2.0 [1.8, 2.3]
Severe renal impairment	8	31.8 [25.6, 39.4]	184 [149, 226]	2.0 [1.5, 2.7]	32.7 [22.6, 40.2]	24.7 [17.3, 35.2]	3.6[a] [2.2, 4.9]

Geometric mean [95% CI]
a n = 7

6.2.5 Drug interactions

6.2.5.1 Drug interaction with rifampicin (Study ID-054-106; CTD 5.3.3.4.2; Study period, July to August 2018)

A 2-treatment, 2-period cross-over study was conducted in 14 healthy adult non-Japanese men (washout period 5 to 7 days). In each period, physiological saline or rifampicin 600 mg was administered intravenously continuously for 30 minutes, immediately followed by continuous intravenous administration of clazosentan for 3 hours at the speed of 15 mg/h. The geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of clazosentan (administered after rifampicin/administered after physiological saline) was 3.13 [2.53, 3.88] and 3.88 [3.24, 4.65], respectively.

6.2.6 Pharmacodynamics

6.2.6.1 QT study (Study ID-054-107; Study CTD 5.3.4.1.3; Study period, September to October 2018)

A 3-treatment, 3-period cross-over study (washout period 3 to 7 days) was conducted in 35 healthy non-Japanese adults to investigate the effect of continuous intravenous administration of clazosentan on QT intervals. In each period, the following regimens were administered:

(a) Continuous intravenous administration of clazosentan for 3 hours at the speed of 20 mg/h, followed by continuous intravenous administration of clazosentan for 3 hours at the speed of 60 mg/h; or
(b) Continuous intravenous administration of placebo for 6 hours; or
(c) A single oral dose of moxifloxacin 400 mg (positive control), immediately followed by continuous intravenous administration of placebo for 6 hours.

When clazosentan was administered intravenously continuously for 3 hours at 20 mg/h, followed by continuous intravenous administration of clazosentan for 3 hours at 60 mg/h, the plasma clazosentan concentration (geometric mean [95% CI]) at 3 or 6 hours after administration was 623 [579, 671] and 1762 [1634, 1900] ng/mL, respectively. During the period of between the start of clazosentan administration at 20 mg/h and 3 hours later, the maximum between-group difference (clazosentan vs. placebo) in the mean change in Fridericia-corrected QT interval (QTcF) from baseline (ΔΔQTcF [90% CI]) was 7.6 [5.00, 10.23] ms, with its upper limit of 90% CI exceeding 10 ms (at 2.5 hours after the start of administration). ΔΔQTcF [90% CI] after the start of clazosentan administration at 60 mg/h was 14.8 [12.13, 17.40] ms at the maximum (at 10 hours after the start of administration), and the upper limit of 90% CI exceeded 10 ms at all evaluation time points between 4 and 12 hours after the start of administration. In the moxifloxacin group, ΔΔQTcF [90% CI] was 12.9 [10.24, 15.50] ms at the maximum, and the lower limit of 90% CI exceeded 5 ms at all evaluation time points between 1.5 and 12 hours after the administration.

ΔΔQTcF reached the maximum level at 10 hours after the start of clazosentan administration, which was later than t_{max} of clazosentan (6 hours after the start of clazosentan) (hysteresis).

6.2.7 Population pharmacokinetic (PPK) analysis

6.2.7.1 Foreign phase III study (Study AC-054-301 [CONSCIOUS-2 Study], CTD 5.3.3.5.1 [Reference data])

A PPK analysis was conducted using plasma clazosentan concentration data at 2284 points obtained from 670 patients with aSAH after clipping in Study AC-054-301.[5)] Plasma concentrations of clazosentan were measured on Days 3 and 9 after the start of administration and at 0 to 2 hours and 2 to 24 hours after the end of administration. PK of clazosentan during the continuous intravenous administration was described by a 2-compartment model with the first-order elimination from the central compartment. Candidate covariates of PK parameters were treatment period, use or non-use of nimodipine (unapproved in Japan) or other concomitant drugs, age (52 [18-75] years) (median

5) A placebo-controlled, parallel-group, double-blind study to investigate the efficacy and safety of clazosentan in patients who underwent clipping for aSAH (phase III study). The primary endpoint was cerebrovascular spasm-associated M/M events up to 6 weeks after the surgery. The study enrolled patients who had diffuse hematoma (major axis ≥20 mm, or extending to both hemispheres) with WFNS grade I to IV before surgery and were able to start receiving the study drug within 56 hours after the onset of aSAH. The target sample size was 1146 patients (assigned at a ratio of 1:2 to receive placebo or clazosentan 5 mg/h) (Study period, December 2007 to July 2010).

[min-max]), body weight (70.0 [41.0-128.0] kg), height (165.0 [137.2-195.0] cm), BMI (24.6 [15.7-48.1] kg/m^2), sex (220 men, 450 women), ethnicity (491 Caucasians/Hispanics, 12 Blacks, 167 Asians), World Federation of Neurosurgical Surgeons (WFNS) grade (I to II in 520, III to V in 150), and study region (Asia in 153, East Europe in 116, North America in 114, Scandinavia in 111, West Europe in 176). In the final PPK model, the following were identified as significant covariates: Sex for distribution volume; and sex, age, ethnicity, and WFNS grade for CL. The population mean parameters (coefficient of variance in %) of the final PPK model was 34.4 L/h (21.1%) (Day 1) and 50.0 L/h (21.1%) (Day 14) for CL, 14.5 L (37.9%) for V_1, and 20.4 L (37.9%) for V_2.

6.2.7.2 Foreign phase III study (Study AC-054-302 [CONSCIOUS-3 Study], CTD 5.3.3.5.2)

PPK analysis was conducted using plasma clazosentan concentration data at 611 points obtained from 174 patients with aSAH after coiling in Study AC-054-302.[6)] Plasma clazosentan concentrations were measured on Days 3 and 9 after the start of clazosentan administration and at 0 to 2 hours and 2 to 24 hours after the end of the administration. PK of clazosentan in continuous intravenous administration was described by a 2-compartment model with consideration given to the time-dependent increase in CL after the start of clazosentan. Candidate covariates of PK parameters were body weight (75.0 ± 19.1 kg [mean ± SD]), age (53.1 ± 10.7 years [mean ± SD]), sex (62 men, 112 women), and WFNS grade (I to II in 148, III to V in 26). In the final PPK model, age was identified as a significant covariate for CL. In the final PPK model, the population mean parameter (coefficient of variance in %) was 25.0 L/h (23.9%) (Day 1) and 39.3 L/h (23.9%) (Day 10) for CL, 15.6 L (69.3%) for V_1, and 16.1 L (37.9%) for V_2.

Using the final PPK model, plasma clazosentan concentration in typical patients aged 30, 50, and 75 years were estimated. Patients aged 30 and 75 years, respectively, had an 8% lower and 7% higher plasma clazosentan concentration than patients aged 50 years.

6.R Outline of the review conducted by PMDA

6.R.1 Similarity of PK between Japanese and South Korean subjects

Results of Study AC-054-202 in patients with aSAH suggest similarity of plasma clazosentan concentration between Japanese and South Korean subjects at time points of the steady state [see Section "6.2.3.1 Japanese and South Korean joint phase II study"]. Accordingly, PMDA considers that the data submitted do not show clinically significant difference in PK of clazosentan between the Japanese and South Korean populations.

6.R.2 QT interval-prolonging effect of clazosentan

The applicant's explanation about QT interval prolongation caused by clazosentan:

In the QT study (Study ID-054-107), following the continuous intravenous administration of clazosentan at 20 or 60 mg/h, the upper limit of 90% CI of ΔΔQTcF exceeded 10 ms at 1 time point (at 2.5 hours) after the start of administration of 20 mg/h and at multiple time points (at 4 to 12 hours)

6) A placebo-controlled, parallel-group, double-blind study to investigate the efficacy and safety of clazosentan in patients who underwent coiling for aSAH (phase III study). The primary endpoint was cerebrovascular spasm-associated M/M events up to Week 6 after the onset of aSAH. The study enrolled patients who had diffuse hematoma (minor axis ≥4 mm) with WFNS grade I to IV before surgery and were able to start receiving the study drug within 56 hours after the onset of aSAH. The target sample size was 1470 patients (assigned at a ratio of 1:1:1 to receive placebo, clazosentan 5 mg/h, or clazosentan 15 mg/h). The study was discontinued when 577 patients were randomized. (Study period, July 2009 to January 2011).

after the start of administration of 60 mg/h. Clazosentan thus prolonged QT-interval. Also, the maximum QT prolongation occurred after t_{max} of clazosentan (hysteresis). ΔΔQTcF peaked at 7.6 [5.00, 10.23] ms in subjects receiving 20 mg/h (at 2.5 hours after the start of administration) and at 14.8 [12.13, 17.40] ms in subjects receiving 60 mg/h (at 10 hours after the start of administration). On the other hand, QTcF of >450 ms and ≤480 ms was observed only in 2 of 36 subjects and ΔQTcF of >30 ms and ≤60 ms only in 1 of 36 subjects, and no subjects had QTcF of >480 ms or ΔQTcF of >60 ms.

Thus, since clazosentan may prolong QT intervals, precautionary advice should be discussed based on the incidences of QT prolongation-related adverse events in clinical studies.

PMDA's view:
Clazosentan was shown to prolong the QT interval in the QT study. Appropriateness of precautionary statements on QT-interval prolongation provided in the package insert should be further discussed based on the incidence of QT interval prolongation-related adverse events such as arrhythmia [see Section "7.R.3.6 Adverse events related to tachyarrhythmia"].

6.R.3 Administration to patients with hepatic impairment

The applicant's explanation about clazosentan administration to patients with hepatic impairment:
In the clinical pharmacology study in subjects with hepatic impairment (Study AC-054-104), the geometric mean ratios [90% CI] of C_{ss} and $AUC_{0-\infty}$, respectively, of clazosentan were as follows:

- 1.35 [1.02, 1.79] and 1.41 [1.04, 1.90] (mild hepatic impairment/normal hepatic function)
- 2.10 [1.59, 2.78] and 2.37 [1.75, 3.19] (moderate hepatic impairment/normal hepatic function)
- 3.20 [2.42, 4.23] and 3.79 [2.81, 5.11] (severe hepatic impairment/normal hepatic function)

The incidence of adverse events in continuous intravenous administration of clazosentan (6 hours at 1.0 mg/h in subjects with normal hepatic function and subjects with mild or moderate hepatic impairment, 3 hours at 0.5 mg/h in subjects with severe hepatic impairment) was 37.5% (3 of 8) of subjects with normal hepatic function, 62.5% (5 of 8) of subjects with mild hepatic impairment, 50.0% (4 of 8) of subjects with moderate hepatic impairment, and 50.0% (4 of 8) of subjects with severe hepatic impairment. A serious adverse event occurred in 1 subject with severe hepatic impairment (hepatic encephalopathy) but resolved. There were no adverse events leading to treatment discontinuation or severe adverse events.

As presented later in Table 16, there was no significant difference in the incidence of adverse events between the clazosentan 1, 5, and 15 mg/h groups in the foreign dose-finding study (Study AC-054-201[7)]). This suggests that the extent of the increase in exposure in subjects with mild hepatic impairment is not clinically important. Also, f_u in subjects with mild hepatic impairment was similar to that in subjects with normal hepatic function. Therefore dose adjustment of clazosentan is not required in subjects with mild hepatic impairment.

7) A placebo-controlled, parallel-group, double-blind study (late phase II study) to investigate the dose-response relationship in patients who underwent clipping or coiling for aSAH. The primary endpoint was moderate or severe cerebrovascular spasm. The study enrolled patients who had diffuse or localized thick hematoma (minor axis ≥4 mm) with WFNS grade I to IV before surgery and were able to start receiving the study drug within 56 hours after the onset of aSAH. The target sample size was 400 patients (assigned at a ratio of 1:1:1:1 to receive placebo, clazosentan 1 mg/h, clazosentan 5 mg/h, or clazosentan 15 mg/h). (Study period, January 2005 to March 2006).

The phase III study in Japanese and non-Japanese patients with aSAH did not include patients with total bilirubin exceeding twice the upper limit of normal of the laboratory range, patients with proven or suspected hepatic cirrhosis, and patients with moderate or severe hepatic impairment. Also, safety of clazosentan was not confirmed in patients with aSAH when administered at a dose exceeding 15 mg/h until Day 15 after aSAH onset. Given the extent of the increase in the exposure in patients with moderate hepatic impairment, it will be necessary to reduce the dose in this patient group.

Table 15 shows the relationship between the dose of clazosentan and efficacy in the dose-finding studies conducted in patients with aSAH in Japan and other countries (Studies AC-054-201 and AC-054-202). Clazosentan is expected to be effective in preventing moderate or severe cerebrovascular spasm at a dose of ≥5 mg/h, while 10 mg/h or a higher dose will be necessary for preventing M/M events.

Table 15. Relationship between clazosentan dose and efficacy in Japanese and foreign dose-finding studies

	Study AC-054-201				Study AC-054-202		
	Placebo	1 mg/h	5 mg/h	15 mg/h	Placebo	5 mg/h	10 mg/h
Moderate or severe cerebrovascular spasm	65.9 (56/85)	43.2 (41/95)	38.9 (37/95)	22.8 (18/79)	80.0 (44/55)	38.5 (20/52)	35.3 (18/51)
M/M event	39.1 (36/92)	37.1 (39/105)	28.3 (30/106)	29.0 (27/93)	47.3 (26/55)	28.8 (15/52)	14.3 (7/49)

Incidence % (number of subjects with events/number of subjects analyzed)

Table 16 shows the relationship between the dose of clazosentan and safety in Studies AC-054-201 and AC-054-202. Some events occurred more frequently in the clazosentan group than in the placebo group, but no adverse events markedly increased with the dose increase from 1 to 15 mg/h.

Table 16. Relationship between clazosentan dose and safety in Japanese and foreign dose-finding studies

	Study AC-054-201				Study AC-054-202		
	Placebo	1 mg/h	5 mg/h	15 mg/h	Placebo	5 mg/h	10 mg/h
All adverse events	95.8 (92/96)	94.4 (101/107)	95.5 (105/110)	95.8 (92/96)	93.3 (56/60)	96.7 (58/60)	94.9 (56/59)
Serious adverse events	45.8 (44/96)	53.3 (57/107)	50.0 (55/110)	52.1 (50/96)	18.3 (11/60)	18.3 (11/60)	16.9 (10/59)
Adverse events of special interest	58.3 (56/96)	66.7 (70/105)	66.7 (74/111)	60.8 (59/97)	48.3 (29/60)	70.0 (42/60)	72.9 (43/59)
Pleural effusion/pulmonary oedema[a]	7.3 (7/96)	20.0 (21/105)	19.8 (22/111)	17.5 (17/97)	10.0 (6/60)	23.3 (14/60)	16.9 (10/59)
Adverse events related to brain oedema[b]	31.3 (30/96)	29.5 (31/105)	25.2 (28/111)	30.9 (30/97)	6.7 (4/60)	18.3 (11/60)	10.2 (6/59)
Other adverse events related to fluid retention[c]	7.3 (7/96)	9.5 (10/105)	10.8 (12/111)	13.4 (13/97)	5.0 (3/60)	11.7 (7/60)	10.2 (6/59)
Adverse events related to cardiac failure[d]	2.1 (2/96)	1.0 (1/105)	0.9 (1/111)	1.0 (1/97)	0.0 (0/60)	0.0 (0/60)	1.7 (1/59)
Adverse events related to hypotension[e]	4.2 (4/96)	8.6 (9/105)	13.5 (15/111)	13.4 (13/97)	1.7 (1/60)	5.0 (3/60)	5.1 (3/59)
Adverse events related to anaemia[f]	20.8 (20/96)	25.7 (27/105)	30.6 (34/111)	19.6 (19/97)	10.0 (6/60)	18.3 (11/60)	18.6 (11/59)
Adverse events related to haemorrhage[g]	18.8 (18/96)	21.0 (22/105)	13.5 (15/111)	16.5 (16/97)	16.7 (10/60)	10.0 (6/60)	11.9 (7/59)
Adverse events related to liver disorder[h]	12.5 (12/96)	10.5 (11/105)	13.5 (15/111)	7.2 (7/97)	26.7 (16/60)	38.3 (23/60)	30.5 (18/59)
Adverse events related to tachyarrhythmia[i]	4.2 (4/96)	6.7 (7/96)	7.2 (8/111)	11.3 (11/97)	1.7 (1/60)	6.7 (4/60)	8.5 (5/59)

Incidence % (number of subjects with events/number of subjects analyzed)

a Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT): Pleural effusion, pulmonary oedema

b PTs belonging to "increased intracranial pressure and hydrocephalus" in MedDRA High level group terms (HLGT)

c PTs belonging to MedDRA Standardised MedDRA queries (SMQ) "haemodynamic oedema, effusions and fluid overload." PTs of swelling of eyelid, swelling face, eyelid oedema, and face oedema were included and PTs of pleural effusion, pulmonary oedema, and brain oedema were excluded.

d PTs belonging to MedDRA SMQ "cardiac failure (narrow)." PT of pulmonary oedema is excluded.

e PTs containing the terms "Blood pressure" and "decreased," PTs containing the term "hypotension" (except intracranial hypotension and neonatal hypotension), PTs of blood pressure immeasurable, mean arterial pressure decreased, and circulatory collapse, and among PTs containing the term "shock," the following PTs were counted: Cardiogenic shock, distributive shock, hypovolaemic shock, procedural shock, shock, shock haemorrhagic, and shock symptom.

f MedDRA SMQ "haematopoietic erythropenia," SMQ "haematopoietic cytopenias affecting more than 1 type of blood cell," PTs containing the term "anaemia," and PT of haemodilution.

g MedDRA SMQ "haemorrhagic central nervous system vascular conditions" were counted. Also, PTs belonging to MedDRA SMQ "haemorrhage terms. (excl laboratory terms)" were counted, except for those corresponding to haemorrhage-related adverse events.

h MedDRA SMQ "hepatic disorders" were counted.

i MedDRA SMQs "tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias)" and "Torsade de pointes/QT prolongation (broad)" were counted.

Given (a) the relationship between the dose of clazosentan and efficacy or safety and (b) the dose-proportional response of clazosentan PK, clazosentan should be administered with care to patients with moderate hepatic impairment at half the normal dose (5 mg/h) to ensure that clazosentan exposure in such patients becomes similar to that in patients with normal hepatic function receiving clazosentan 10 mg/h.

Clazosentan should be contraindicated in patients with severe hepatic impairment not only because of the increased exposure but also because (a) ERA, the drug class to which clazosentan belongs, may induce hepatic dysfunction, and (b) patients with severe hepatic impairment may experience an abrupt change in disease condition after aSAH.

PMDA's view:

Administration to patients with mild hepatic impairment

The applicant's opinion that no dose adjustment is necessary in this patient group is appropriate, given the extent of the increase in clazosentan exposure observed in Study AC-054-104 and the demonstrated safety following the administration at 15 mg/h until Day 15 after aSAH onset.

Administration to patients with moderate hepatic impairment

Given the extent of clazosentan exposure observed in Study AC-054-104, clazosentan administered at the usual dose (10 mg/h) to patients with moderate hepatic impairment is expected to result in an exposure level of unknown safety (i.e., the safety of the exposure level has not been evaluated in clinical studies in patients with aSAH). This suggests the necessity of dose reduction in patients with moderate hepatic impairment from the aspect of pharmacokinetics and safety. The applicant discussed that, in order to prevent M/M events, plasma clazosentan concentration should be maintained at the same level as that achieved by clazosentan 10 mg/h, based on the results of the Japanese and foreign dose-finding studies (Studies AC-054-201 and AC-054-202). Given this discussion, clazosentan at half the usual dose (5 mg/h) is expected to be effective in patients with moderate hepatic impairment. However, there are no clinical data on the efficacy and safety of clazosentan 5 mg/h in patients with moderate hepatic impairment. Physicians should be advised to carefully decide whether to administer clazosentan to such patients, and should be advised to reduce the dose to 5 mg/h, half the usual dose, when administering clazosentan to such patients. Information on the efficacy and safety in patients with moderate hepatic impairment should be collected after the market launch.

Administration to patients with severe hepatic impairment

The applicant's proposal to contraindicate clazosentan in this patient group is appropriate, given (a) the extent of the increase in clazosentan exposure in patients with severe hepatic impairment, (b) the risk of clazosentan-induced hepatic dysfunction, and (c) the possibility of abrupt change in clinical conditions after aSAH onset.

Appropriateness of the above conclusion by PMDA will be determined, also taking account of comments raised in the Expert Discussion.

6.R.4 Co-administration of an OATP1B1/1B3 inhibitor with clazosentan

The applicant's explanation about the co-administration of an OATP1B1/1B3 inhibitor with clazosentan:

In the drug interaction study of rifampicin, an OATP1B1/1B3 inhibitor, in healthy non-Japanese adults (Study ID-054-105), the geometric mean ratio [90% CI] of C_{max} and $AUC_{0-\infty}$ of clazosentan (clazosentan + rifampicin / clazosentan alone) was 3.13 [2.53, 3.88] and 3.88 [3.24, 4.65], respectively. There are no pharmacokinetic data on the co-administration of clazosentan with OATP1B1/1B3 inhibitors other than rifampicin, and it is difficult to predict (a) the extent of OATP1B1/1B3 inhibition or (b) the extent of the increase in the exposure to clazosentan in combination with other OATP1B1/1B3 inhibitors, even from the information available from published reports. However, there is no significant difference in K_i and IC_{50} between rifampicin and ciclosporin, a compound described as a typical OATP1B1/1B3 inhibitor, according to "Guidelines on Drug Interaction for Drug

Development and Appropriate Provision of Information: PSEHB/PED Notification No. 0723-4, dated July 23, 2018." This suggests that the extent of an increase in the exposure to clazosentan in combination with ciclosporin is probably similar to that in combination with rifampicin. Co-administration of clazosentan and OATP1B1/1B3 inhibitors is expected to cause a significant increase in clazosentan exposure, and Japanese and foreign clinical studies in patients with aSAH excluded patients who required co-administration of potent OATP1B1/1B3 inhibitors (ciclosporin A, rifampicin, lopinavir/ritonavir combination drug, etc.). In routine clinical practice, however, there may be patients with aSAH and a concurrent disease requiring treatment with a OATP1B1/1B3 inhibitor, and there may be cases where there is no choice but to co-administer clazosentan and an OATP1B1/1B3 inhibitor (e.g., co-administration of ciclosporin A to patients who experienced aSAH after organ transplantation, co-administration of atazanavir or lopinavir/ritonavir to patients with HIV who experienced aSAH). Therefore the co-administration need not be contraindicated, provided that the dose reduction of clazosentan is considered.

When clazosentan is used in combination with a OATP1B1/1B3 inhibitor, physicians should be advised to carefully use clazosentan by considering its dose reduction (e.g., to 2.5 mg/h [a quarter of the normal dose]) to achieve clazosentan exposure similar to those achieved by clazosentan 10 mg/h alone, taking account of the following points:

(a) The safety of clazosentan administered to patients with aSAH at a dose exceeding 15 mg/h until Day 15 after aSAH onset, has not been confirmed.
(b) The relationship between the dose of clazosentan and efficacy or safety described in Section "6.R.3 Administration to patients with hepatic impairment."

PMDA's view:
Basically, clazosentan should not be co-administered with a OATP1B1/1B3 inhibitor, considering (a) the extent of the increase in exposure to clazosentan administered with rifampicin in Study ID-054-106 and (b) the unavailability of clinical study data on the efficacy and safety of clazosentan in combination with a OATP1B1/1B3 inhibitor. If such a co-administration is unavoidable, particularly when clazosentan has to be used with rifampicin, the dose of clazosentan should be reduced to ensure the safety. Clazosentan is expected to be effective when administered at a quarter of the usual dose (at 2.5 mg/h) in combination with rifampicin, judging from the results of discussion in Section "6.R.3 Administration to patients with hepatic impairment." The applicant explained that the extent of increase in the exposure to clazosentan in combination with an OATP1B1/1B3 inhibitor other than rifampicin was estimated to be similar to that to clazosentan in combination with rifampicin, based on the similarity of K_i or IC_{50}. However, it is difficult to predict the extent of the increase in clazosentan exposure in humans from the *in vitro* data (K_i or IC_{50}) alone. Accordingly, it is impossible to estimate the appropriate dose of clazosentan in combination with OATP1B1/1B3 inhibitors other than rifampicin.

Based on the above, the Precautions for co-administration section of the package insert should include the following statements:

(a) Co-administration with OATP1B1/1B3 inhibitors should be avoided except in therapeutically inevitable cases.

(b) If co-administration with rifampicin is unavoidable, the dose of clazosentan should be reduced to a quarter of the usual dose (i.e., 2.5 mg/h).
(c) If co-administration of OATP1B1/1B3 inhibitors other than rifampicin is unavoidable, the physician should consider reducing the dose of clazosentan, and carefully monitor the clinical condition of the patient for any possible adverse drug reactions.

Appropriateness of the above conclusion by PMDA will be determined, also taking account of comments raised in the Expert Discussion.

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

The applicant submitted main efficacy and safety evaluation data from 3 studies shown in Table 17. In all of these studies, the dose of clazosentan sodium is expressed as the equivalent dose of clazosentan.

Table 17. Summary of main clinical studies on efficacy and safety

Category	Region	Study code	Phase	Population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Japan and South Korea	AC-054-202	II	Patients who underwent clipping for aSAH	179	Within 56 hours after aSAH onset, intravenous administration of clazosentan 5 mg/h, 10 mg/h or placebo was started and continued until Day 14 after aSAH onset.	Efficacy Safety
	Japan	AC-054-306	III	Patients who underwent clipping for aSAH	220	Within 48 hours after aSAH onset, intravenous administration of clazosentan 10 mg/h or placebo was started and continued for a maximum of 15 days after aSAH onset.	Efficacy Safety
	Japan	AC-054-305	III	Patients who underwent coiling for aSAH	220	Within 48 hours after aSAH onset, intravenous administration of clazosentan 10 mg/h or placebo was started and continued for a maximum of 15 days after aSAH onset.	Efficacy Safety

7.1 Phase II study

7.1.1 Japanese and South Korean joint phase II study (Study AC-054-202; CTD 5.3.5.1.3; Study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel-group study was conducted to investigate the cerebrovascular spasm-suppressing effect and safety of clazosentan in patients who had undergone clipping for aSAH (target sample size, 168[8)]) at 32 study sites in Japan and South Korea.

Intravenous administration of placebo, clazosentan 5 mg/h, or clazosentan 10 mg/h was started within 56 hours after aSAH onset and continued until Day 14 after aSAH onset. Solution containing clazosentan 150 mg (25 mg/mL) or syringe filled with 6 mL solution was diluted with 500 mL

8) The incidence of cerebrovascular spasm in the placebo group and in the clazosentan group was assumed to be 80% and 44%, respectively, by reference to the incidence in the foreign phase IIa study (Study AXV-034-2S01) and phase IIb study (Study AC-054-201). The required sample size was estimated to be 48 subjects per group to detect a statistically significant difference between any clazosentan group and the placebo group by a χ^2 test (two-sided significance level of 5%, statistical power 0.9), corrected for statistical multiplicity by Bonferroni-Holm method. By assuming the dropout rate of 15%, 56 subjects were enrolled per group.

physiological saline. The diluted solution was administered at the speed of 17 mL/h (5 mg/h clazosentan or 10 mg/h clazosentan).

The investigator was instructed to consider rescue therapies shown in Table 18 in cases where:

- Lucid patients show any clinical finding suggesting cerebrovascular spasm (somnolence, pyrexia, ≥2-point decrease in modified Glasgow Coma Scale [mGCS], ≥2-point increase in simple National Institutes of Health Stroke Scale [NIHSS] score, etc.); or
- Digital subtraction angiography (DSA) reveals cerebrovascular spasm in sedated or consciousness-disturbed patients despite absence of clinical findings suggesting cerebrovascular spasm.

Table 18. Rescue therapies against cerebrovascular spasm

Rescue therapies that could be used (new start or dose increase) in combination with study drug	Rescue therapies requiring discontinuation of study drug
• Increase in circulating blood volume • Hemodilution • Artificial hypertension • Percutaneous transluminal angioplasty • Intra-arterial administration of a vasodilator (fasudil hydrochloride hydrate, ozagrel sodium, papaverine hydrochloride, verapamil hydrochloride, etc.) or an antiplatelet agent within 15 minutes after percutaneous transluminal angioplasty, etc.	• Intravenous administration of a vasodilator, an antiplatelet agent, etc. • Continuous intravenous administration of magnesium • Administration of an HMG-CoA reductase inhibitor

Co-administration of the following drugs with the study drug was prohibited: Intravenous administration of nimodipine (unapproved in Japan), intravenous administration of nicardipine, fasudil hydrochloride hydrate, ozagrel sodium, nizofenone fumarate, ticlopidine hydrochloride, intravenous administration of magnesium (for the prevention of cerebrovascular spasm), HMG-CoA reductase inhibitors (subjects who were using a HMG-CoA reductase inhibitor before the start of study were allowed to continue using the drug), thrombolytic drugs, antiplasmin agents, cyclosporine A and other calcineurin inhibitors, intravenous administration of alteplase, and approved ERAs.

Table 19 shows the main inclusion and exclusion criteria.

Table 19. Main inclusion and exclusion criteria of Study AC-054-202

Inclusion criteria	Exclusion criteria
• Patients with aSAH aged ≥20 and ≤75 years • The timing of aneurysm rupture is known or can be guessed. • CT before clipping revealed Fisher group 3 SAH regardless of intracranial or intraventricular hematoma, and subarachnoidal hematoma is ≥20 mm (long axis) or extends to both hemispheres. • WFNS grade I to IV before clipping • WFNS grade I to IV after clipping[a] • DSA before clipping revealed saccular aneurysm and clipping succeeded.[b]	• aSAH due to a cause other than saccular aneurysm (traumatic aneurysm, fusiform ruptured aneurysm, mycotic aneurysm, etc.) • DSA before clipping revealed cerebrovascular spasm. • Patients with serious intraoperative complications (massive haemorrhage, occlusion of major artery, large territorial cerebral infarction involving ≥1/3 of vascular area) • Serious neurological disorders (hemiplegia, disturbance in consciousness, aphasia, etc.) newly occurred after clipping and is persisting at ≥12 hours after clipping • Patients unable to receive diagnostic imaging and other tests stipulated by the clinical study protocol • Treatment-resistant hypotension (systolic blood pressure <90 mmHg at the screening test) • Pneumonia aspiration or pulmonary oedema • Severe cardiac failure requiring inotropic support • Renal or hepatic disease (serum creatinine level ≥2.0 mg/dL [≥177 μmol/L] or total bilirubin more than twice the upper limit of normal of the laboratory range at screening), or confirmed or suspected hepatic cirrhosis

a If post-clipping WFNS grade could not be evaluated because of increased or unstable post-clipping intracranial pressure requiring continued sedation, the absence of large territorial cerebral infarction (covering ≥1/3 of the vascular territory) was confirmed by CT performed ≥12 hours after clipping before randomization.
b Patients who underwent both clipping and coiling could be enrolled.

Of 181 randomized subjects (60 in the placebo group, 61 in the clazosentan 5 mg/h group, 60 in the clazosentan 10 mg/h group), 179 subjects (59 in the placebo group [35 Japanese], 61 in the clazosentan 5 mg/h group [35 Japanese], 59 in the clazosentan 10 mg/h group [35 Japanese]) were included in the All Treated Set, which was handled as the safety analysis set.[9)] The remaining 2 subjects were excluded because they did not receive the study drug. Among the subjects in the All Treated Set, 158 subjects (55 in the placebo group [34 Japanese], 52 in the clazosentan 5 mg/h group [29 Japanese], 51 in the clazosentan 10 mg/h group [32 Japanese]) were included in the Per Protocol Set (PPS) and handled as the primary efficacy analysis set. The remaining 21 subjects were excluded for reasons including "DSA was not performed" "DSA was performed outside the specified time window," "DSA image was inadequate," and "prohibited concomitant drugs were used." Treatment discontinuation occurred in 19 subjects (8 in the placebo group, 7 in the clazosentan 5 mg/h group, 4 in the clazosentan 10 mg/h group). Main reasons for the discontinuation were adverse events in 13 subjects (3, 6, 4) and administration of prohibited concomitant drugs in 3 subjects (2, 1, 0). The duration of the study drug administration (median [min, max]) was 11.96 [0.9, 13.7] days in the placebo group, 12.00 [2.9, 14.0] days in the clazosentan 5 mg/h group, and 11.98 [2.9, 14.0] days in the clazosentan 10 mg/h group.

Table 20 shows the incidence of moderate or severe cerebrovascular spasm up to Day 14 after aSAH onset,[10)] which was evaluated as the primary endpoint in the entire population and in the Japanese population. In the entire population, the incidence of moderate or severe cerebrovascular spasm was significantly lower in both clazosentan groups than in the placebo group.

9) One subject was assigned to [redacted] group but actually received [redacted] in error. The subject was included in [redacted] group in the safety analysis set and in [redacted] group in the efficacy analysis set.
10) DSA was conducted at screening, on Day 9 ± 2 after aSAH onset, and at arbitrary points by Day 14 after aSAH onset (in cases of DIND, clinical symptoms suggesting cerebrovascular spasm, suspected new or aggravated cerebral infarction). Cerebrovascular spasm was rated by an independent central assessment committee based on the rate of decrease in the inner arterial diameter relative to baseline DSA image (before clipping), as follows: a 0% to 33% decrease as "no or mild" vasospasm; a 34% to 66% decrease as "moderate" vasospasm; and a 67% to 100% decrease as "severe" vasospasm.

Table 20. Incidence of moderate or severe cerebrovascular spasm occurring within 14 days after aSAH (PPS)

	Placebo	Clazosentan	
		5 mg/h	10 mg/h
Entire population	80.0 (44/55) [67.0, 89.6]	38.5 (20/52) [25.3, 53.0]	35.3 (18/51) [22.4, 49.9]
P value[a]	-	<0.0001	<0.0001
Japanese population	79.4 (27/34) [62.1, 91.3]	44.8 (13/29) [26.4, 64.3]	25.0 (8/32) [11.5, 43.4]

Incidence % (number of subjects with events/number of subjects analyzed) [exact 95% CI]; -, Not applicable
a Fisher's exact test (statistical multiplicity adjusted for by Bonferroni-Holm correction), comparison with the placebo group

The incidence of cerebrovascular spasm-associated new or aggravated cerebral infarction occurring within 6 weeks after aSAH onset,[11)] the secondary endpoint, was 20.8% (11 of 53) of subjects in the placebo group, 3.8% (2 of 52) of subjects in the clazosentan 5 mg/h group, and 4.2% (2 of 48) of subjects in the clazosentan 10 mg/h group.

An exploratory endpoint was cerebrovascular spasm-associated events (Morbidity) or death of all causes (Mortality) (hereinafter referred to as "M/M events") occurring within 6 weeks after aSAH onset and their components. Table 21 shows the incidence of these events.

Table 21. Incidence of M/M events within 6 weeks after onset of aSAH (PPS)

	Placebo (n = 55)	Clazosentan 5 mg/h (n = 52)	Clazosentan 10 mg/h (n = 51)
M/M events	47.3 (26/55)	28.8 (15/52)	14.3 (7/49)
All-cause deaths	1.8 (1/55)	0 (0/52)	2.0 (1/51)
Cerebrovascular spasm-associated new or aggravated cerebral infarction	20.8 (11/53)	3.8 (2/52)	4.2 (2/48)
Cerebrovascular spasm-associated DIND	32.7 (18/55)	19.2 (10/52)	11.8 (6/51)
Initiation of rescue therapy against cerebrovascular spasm	27.3 (15/55)	13.5 (7/52)	5.9 (3/51)

Incidence % (number of subjects with events/number of subjects analyzed)

The incidence of adverse events[12)] in the entire population was 93.3% (56 of 60) of subjects in the placebo group, 96.7% (58 of 60) of subjects in the clazosentan 5 mg/h group, and 94.9% (56 of 59) of subjects in the clazosentan 10 mg/h group. Table 22 shows adverse events with an incidence of ≥10% in any group. In the Japanese population, the incidence of adverse events was 91.4% (32 of 35) of subjects in the placebo group, 94.3% (33 of 35) of subjects in the clazosentan 5 mg/h group, and 94.3% (33 of 35) of subjects in the clazosentan 10 mg/h group. Table 23 shows adverse events with an incidence of ≥10% in any group.

11) CT was performed at screening, 24 to 48 hours after clipping, and 6 and 12 weeks after the onset of aSAH. The occurrence of new or aggravated cerebral infarction and its relationship to cerebrovascular spasm was assessed under blinded conditions by an independent central assessment committee.
12) Adverse events occurring within 24 hours after discontinuation or completion of study drug administration.

Table 22. Adverse events with an incidence of ≥10% in any group (safety analysis set [entire population])

MedDRA PT	Placebo (n = 60)	Clazosentan	
		5 mg/h (n = 60)	10 mg/h (n = 59)
Headache	23.3 (14)	21.7 (13)	25.4 (15)
Cerebral vasoconstriction	56.7 (34)	33.3 (20)	18.6 (11)
Hypokalaemia	15.0 (9)	16.7 (10)	18.6 (11)
γ-GTP increased	6.7 (4)	8.3 (5)	16.9 (10)
Pyrexia	26.7 (16)	21.7 (13)	15.3 (9)
Constipation	20.0 (12)	20.0 (12)	13.6 (8)
Anaemia	10.0 (6)	18.3 (11)	13.6 (8)
ALT increased	13.3 (8)	11.7 (7)	13.6 (8)
Hyponatraemia	15.0 (9)	11.7 (7)	13.6 (8)
Nausea	11.7 (7)	10.0 (6)	13.6 (8)
AST increased	11.7 (7)	11.7 (7)	11.9 (7)
Vomiting	11.7 (7)	11.7 (7)	11.9 (7)
Pleural effusion	5.0 (3)	8.3 (5)	11.9 (7)
Confusional state	1.7 (1)	10.0 (6)	6.8 (4)
Brain oedema	0 (0)	10.0 (6)	6.8 (4)
Pulmonary oedema	5.0 (3)	16.7 (10)	5.1 (3)
Hepatic function abnormal	5.0 (3)	10.0 (6)	3.4 (2)

Incidence % (number of subjects with events)

Table 23. Adverse events with an incidence of ≥10% in any group (safety analysis set [Japanese population])

MedDRA PT	Placebo (n = 35)	Clazosentan	
		5 mg/h (n = 35)	10 mg/h (n = 35)
Anaemia	8.6 (3)	14.3 (5)	11.4 (4)
Eyelid oedema	0 (0)	2.9 (1)	11.4 (4)
Constipation	8.6 (3)	11.4 (4)	11.4 (4)
Pyrexia	17.1 (6)	14.3 (5)	8.6 (3)
Hepatic function abnormal	8.6 (3)	17.1 (6)	5.7 (2)
γ-GTP increased	11.4 (4)	11.4 (4)	22.9 (8)
ALT increased	14.3 (5)	8.6 (3)	17.1 (6)
AST increased	11.4 (4)	8.6 (3)	14.3 (5)
Hyponatraemia	2.9 (1)	14.3 (5)	8.6 (3)
Hypokalaemia	14.3 (5)	11.4 (4)	5.7 (2)
Headache	22.9 (8)	25.7 (9)	22.9 (8)
Delayed ischaemic neurological deficit	37.1 (13)	25.7 (9)	14.3 (5)
Cerebral vasoconstriction	51.4 (18)	25.7 (9)	11.4 (4)
Brain oedema	0 (0)	11.4 (4)	8.6 (3)
Cerebral infarction	14.3 (5)	8.6 (3)	5.7 (2)
Pleural effusion	8.6 (3)	11.4 (4)	14.3 (5)
Pulmonary oedema	2.9 (1)	20.0 (7)	5.7 (2)

Incidence % (number of subjects with events)

The incidence of adverse events that occurred within 12 weeks after aSAH onset and led to death was 1.7% (1 of 60 subjects; carotid artery occlusion/cerebral vasoconstriction) in the placebo group, 1.7% (1 of 60 subjects; cerebral infarction) in the clazosentan 5 mg/h group, and 3.4% (2 of 59 subjects; cerebral infarction in 2 subjects) in the clazosentan 10 mg/h group. All events were considered to be unrelated to the study drug. In the Japanese population, the incidence of adverse events leading to death was 2.9% (1 of 35 subjects: cerebral infarction) in the clazosentan 5 mg/h group and 2.9% (1 of 35 subjects; cerebral infarction) in the clazosentan 10 mg/h group. These events were considered to be unrelated to the study drug.

The incidence of serious adverse events that occurred within 6 weeks after aSAH onset was 18.3% (11 of 60) of subjects in the placebo group, 18.3% (11 of 60) of subjects in the clazosentan 5 mg/h group, and 16.9% (10 of 59) of subjects in the clazosentan 10 mg/h group. Events with an incidence of ≥3% in any group was cerebral infarction (0% in the placebo group, 3.3% in the clazosentan 5 mg/h group, 6.8% in the clazosentan 10 mg/h group), hydrocephalus (3.3%, 3.3%, 3.4%), brain oedema (0%, 6.7%, 1.7%), intracranial aneurysm (3.3%, 1.7%, 1.7%), and cerebral vasoconstriction (5.0%, 1.7%, 0%). Among the events observed, extradural haematoma and brain oedema in 1 subject each in the clazosentan 5 mg/h group and cardiac failure and platelet count decreased in 1 subject each in the clazosentan 10 mg/h group were considered to be related to the study drug. In the Japanese population, the incidence of serious adverse events that occurred within 6 weeks after aSAH onset was 2.9% (1 of 35) of subjects in the placebo group, 14.3% (5 of 35) of subjects in the clazosentan 5 mg/h group, and 11.4% (4 of 35) of subjects in the clazosentan 10 mg/h group. Events with an incidence of ≥5% in any group were cerebral infarction (0% in the placebo group, 2.9% in the clazosentan 5 mg/h group, 5.7% in the clazosentan 10 mg/h group) and brain oedema (0%, 8.6%, 2.9%). Among the events observed, extradural haematoma and brain oedema in 1 subject each in the clazosentan 5 mg/h group and cardiac failure and platelet count decreased in 1 subject each in the clazosentan 10 mg/h group were considered to be related to the study drug.

The incidence of adverse events leading to discontinuation of the study drug was 8.3% (5 of 60) of subjects in the placebo group, 10.0% (6 of 60) of subjects in the clazosentan 5 mg/h group, and 6.8% (4 of 59) of subjects in the clazosentan 10 mg/h group. The event with an incidence of ≥3% in any group was cerebral vasoconstriction (8.3% in the placebo group, 6.7% in the clazosentan 5 mg/h group, 0% in the clazosentan 10 mg/h group). In the Japanese population, the incidence of adverse events leading to discontinuation of the study drug was 5.7% (2 of 35) of subjects in the placebo group, 17.1% (6 of 35) of subjects in the clazosentan 5 mg/h group, and 8.6% (3 of 35) of subjects in the clazosentan 10 mg/h group. The event with an incidence of ≥5% in any group was cerebral vasoconstriction (5.7% in the placebo group, 11.4% in the clazosentan 5 mg/h group, 0% in the clazosentan 10 mg/h group).

7.2 Phase III studies

7.2.1 Japanese phase III study (Study AC-054-306; CTD 5.3.5.1.7; Study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel-group study was conducted to investigate the effect of clazosentan in preventing M/M events in patients who had undergone clipping for aSAH (target sample size, 220 subjects) at 46 study sites in Japan. The initial target sample size was 160[13)] and, when 160 subjects were enrolled, the incidence of M/M events was reviewed under blinded conditions in 80 subjects who had completed the assessment by the imaging review committee, the event assessment committee, and the hematoma mass subcommittee. The results showed that the incidence

[13)] By reference to the incidence of cerebrovascular spasm-associated M/M events except "initiation of rescue therapy" in the Japanese and South Korean joint phase II study (Study AC-054-202), the incidence of M/M events in the placebo group and the clazosentan group was assumed to be 39% and 17%, respectively, and the required sample size was estimated to be 77 subjects per group to detect a statistically significant between-group difference by Cochran-Mantel-Haenszel test (two-sided significance level of 5%, statistical power 0.9). Under these assumptions, the statistical power of the hypothesis test based on the hierarchical closed testing procedure was 0.90 for the primary endpoint (1) and 0.87 for the primary endpoint (2). By assuming the number of subjects excluded from FAS to be 3 per group, the target sample size was determined to be 80 per group.

of M/M events was 20%, which was lower than the level assumed at the study planning (28%); this suggested that the statistical power was as low as approximately 71%. Accordingly, the target sample size was re-estimated. Thus, by assuming the incidence of M/M events to be 27.9% in the placebo group and 12.1% in the clazosentan group, 110 subjects per group were estimated to be required for detecting the treatment effect (relative risk reduction rate) of approximately 43% at the statistical power of 84%.[14)]

Intravenous administration of placebo or clazosentan was started as soon as possible within 48 hours after aSAH onset, and was continued until Day 14 after the onset (for 15 days at the longest). The content of 2 vials (each vial was filled with a 6 mL solution containing clazosentan 150 mg [25 mg/mL]) was diluted with 500 mL physiological saline. The diluted solution was administered at the speed of 17 mL/h (10 mg/h of clazosentan). During the period between the study drug administration and Week 6 after aSAH onset, the subjects could receive rescue therapies for cerebrovascular spasm shown in Table 24 in order to ensure their safety.

Table 24. Rescue therapies for cerebrovascular spasm

Rescue therapies that could be used in combination with study drug	Rescue therapy requiring discontinuation of study drug
• Initiation of, or dose increase or change in, Triple H therapy (hypervolemia, hemodilution, hypertension)[a] • Hyperdynamic therapy (initiation of, or increase in dose of, dobutamine administration) • Percutaneous transluminal angioplasty • Intrathecal/cisternal administration of nicardipine • Intra-arterial administration of vasodilators (fasudil hydrochloride hydrate, papaverine hydrochloride, milrinone, ozagrel sodium, etc.) within 15 minutes	• Initiation of intravenous administration of a vasodilator, an antiplatelet agent, etc.

a The increase in infusion volume was to be avoided whenever possible.

Concomitant use of the following drugs was prohibited.

(1) During the period of study drug administration after aSAH onset:
- Ticlopidine hydrochloride
- Intra-arterial administration of fasudil hydrochloride hydrate, ozagrel sodium, milrinone, and papaverine hydrochloride
- Intrathecal/cisternal administration of nicardipine hydrochloride

(2) For 4 hours before and during the period of study drug administration
- Intravenous administration of fasudil hydrochloride hydrate, ozagrel sodium, milrinone, and nicardipine hydrochloride

(3) During the period of study drug administration
- Intravenous administration of cilostazol, edaravone, and magnesium (off-label use for the prevention of cerebrovascular spasm or for improving prognosis after aSAH was prohibited, but use for approved indications was permitted)
- HMG-CoA reductase inhibitors (permitted if they had been used from before the onset of aSAH)
- Thrombolytic agents (including intrathecal/cisternal administration), antiplasmin agents (tranexamic acid, etc.)

14) Under these assumptions, the statistical power of the hypothesis test based on the hierarchical closed testing procedure was 84% for the primary endpoint (1) and 83% for the primary endpoint (2).

- Hypertonic saline (use for treatment of hyponatremia or increased intracranial pressure was permitted)
- Cyclosporine A, rifampicin, lopinavir/ritonavir combination drug
- Approved ERAs

Table 25 shows the main inclusion and exclusion criteria. The study was conducted by dynamic allocation procedure (allocation ratio 1:1) according to the WFNS grade (I, II, III, and IV).

Table 25. Main inclusion and exclusion criteria of Study 306

Inclusion criteria	Exclusion criteria
• Patients aged ≥20 and ≤75 years • DSA revealed saccular aneurysm and clipping succeeded. • The timing of aneurysm rupture is known or can be guessed. • CT before clipping revealed Fisher grade 3 SAH • WFNS grade I to IV before clipping If ventricular drainage is required because of hydrocephalus, etc., grading should be performed after the drainage. • WFNS grade I to IV after clipping When WFNS grading could not be performed because of sedation, etc., the absence of clipping-associated large territorial cerebral infarction (affecting ≥1/3 of the vascular territory) was confirmed by CT before randomization after clipping. • Blood pressure and transfusion can be controlled according to the patient management guidelines.	• aSAH due to a cause other than saccular aneurysm (traumatic aneurysm, ruptured fusiform aneurysm, mycotic aneurysm, arteriovenous malformation, etc.) • Moderate or severe cerebrovascular spasm detected by DSA before clipping • Serious intraoperative complications (massive haemorrhage, occlusion of major artery, cerebrovascular dissection, vascular injury, large territorial cerebral infarction involving ≥1/3 of vascular territory, etc.) • Serious neurological disorders (hemiplegia, disturbance in consciousness, aphasia, etc.) newly occurred after clipping and is still persisting at ≥12 hours after clipping • Patients unable to receive diagnostic imaging and other tests stipulated by the clinical study protocol • Patients who received intra-arterial administration of a prophylactic or therapeutic vasodilator or who are scheduled to undergo percutaneous transluminal angioplasty • Patients who received a stent in the intracranial major artery before the start of study drug administration • Treatment-resistant hypotension (systolic blood pressure <90 mmHg at screening) • Pulmonary oedema or severe pneumonia • Severe cardiac failure requiring inotropic support Severe hypoxia [PaO2/FiO2 <250 mmHg] under artificial ventilation • Intracranial pressure >25 mmHg for ≥20 minutes in patients with ICP monitor • mRS >3 before the onset of aSAH • Total bilirubin more than twice the upper limit of normal of the laboratory range, confirmed or suspected cirrhosis, or moderate or severe hepatic impairment • Patients who received an unapproved drug or treatment (e.g., intra-aortic balloon) to improve prognosis or ischemic condition after aSAH

Of 221 randomized subjects (112 in the placebo group, 109 in the clazosentan group), 220 subjects (111 in the placebo group, 109 in the clazosentan group) were included in the full analysis set (FAS) and the safety analysis set (the remaining 1 subject who did not receive the study drug was excluded). The FAS was handled as the primary efficacy analysis set. Study discontinuation within 12 weeks after aSAH onset occurred in 14.3% (16 of 112) of subjects in the placebo group and 15.6% (17 of 109) of subjects in the clazosentan group. Main reasons for the discontinuation were use of prohibited concomitant drugs in 10 subjects (6 in the placebo group, 4 in the clazosentan group), adverse events in 9 subjects (4, 5), and extensive brain oedema or severe pulmonary oedema in 6 subjects (2, 4). The duration of the study drug administration (median [min., max.]) was 12.47 [0.2, 13.1] days in the placebo group and 12.01 [1.2, 14.0] days in the clazosentan group.

Presence (≥1 site) or absence of moderate or severe cerebrovascular spasm, occurrence of new cerebral infarction, and the relationship between cerebrovascular spasm and the new cerebral infarction were evaluated based on DSA and computed tomography (CT) images by the central imaging review committee under blinded conditions. Presence or absence of DIND, appropriateness of starting rescue therapy, and the relationship between cerebrovascular spasm and death, new cerebral infarction (when DSA or CT image was unavailable), DIND, and initiation of rescue therapy was evaluated by the event assessment committee under blinded conditions.

Efficacy was evaluated based on 2 primary endpoints:

Primary endpoint (1): Cerebrovascular spasm-associated M/M events occurring between the start of study drug administration and Week 6 after aSAH onset.

Primary endpoint (2): All-cause M/M events occurring between the start of study drug administration and Week 6 after aSAH onset.

Table 26 shows the results of the primary endpoints and their components. The incidence of cerebrovascular spasm-associated M/M events, the primary endpoint (1), was significantly lower in the clazosentan group than in the placebo group. Since a significant between-group difference was observed in the primary endpoint (1), the results of the primary endpoint (2) were analyzed based on the hierarchical closed testing procedure. No significant difference was observed in the incidence of all-cause M/M events between the clazosentan and placebo groups.

Table 26. Incidence of M/M events within 6 weeks after aSAH onset (FAS)

	Placebo (n = 111)	Clazosentan (n = 109)	Between-group difference [exact 95% CI]	*P* value[a]
Primary endpoint (1)				
Cerebrovascular spasm-associated M/M events	39.6 (42/106[b])	16.2 (17/105[b])	−23.4 [−36.4, -10.3]	0.0001
All-cause deaths	1.8 (2/111)	0.9 (1/109)		
Cerebrovascular spasm-associated new cerebral infarction	33.3 (36/108[b])	12.3 (13/106[b])		
Cerebrovascular spasm-associated DIND	21.3 (23/108[b])	8.4 (9/107[b])		
Primary endpoint (2)				
All-cause M/M events	57.5 (61/106[b])	45.7 (48/105[b])	−11.8 [−25.3, 2.0]	0.0880
All-cause deaths	1.8 (2/111)	0.9 (1/109)		
New cerebral infarction	50.0 (54/108[b])	37.7 (40/106[b])		
DIND	30.6 (33/108[b])	23.4 (25/107[b])		

Incidence % (number of subjects with events/number of subjects analyzed)

a Cochran-Mantel-Haenszel test with the covariate of WFNS grade (4 grades) before clipping (two-sided significance level of 5%). First, the primary endpoint (1) was to be subjected to test according to the hierarchical closed testing procedure and, only when a between-group difference was observed, the primary endpoint (2) was to be subjected to the test.

b The analysis of the presence/absence of cerebrovascular spasm and new cerebral infarction excluded subjects who did not receive DSA and CT (including unspecified test) by Week 6 and subjects unevaluable for DIND until Week 6.

The incidence of moderate or severe cerebrovascular spasm within 14 days after aSAH onset (the secondary endpoint) was 55.0% (61 of 111) of subjects in the placebo group and 24.8% (27 of 109) of subjects in the clazosentan group.

Rescue therapy that could be used in combination with the study drug was performed in 26.1% (29 of 111) of subjects in the placebo group and 9.2% (10 of 109) of subjects in the clazosentan group.

Rescue therapy requiring discontinuation of the study drug was performed in 11.7% (13 of 111) of subjects in the placebo group and 7.3% (8 of 109) of subjects in the clazosentan group.

The incidence of adverse events that occurred between the start of study drug administration and 30 days after the completion (discontinuation) of administration was 96.4% (107 of 111) of subjects in the placebo group and 99.1% (108 of 109) of subjects in the clazosentan group. Table 27 shows adverse events with an incidence of ≥10% in either group.

Table 27. Adverse events with an incidence of ≥10% in either group (safety analysis set)

MedDRA PT	Placebo (n = 111)	Clazosentan (n = 109)
Constipation	43.2 (48)	36.7 (40)
Hyponatraemia	25.2 (28)	29.4 (32)
Delayed ischaemic neurological deficit	30.6 (34)	22.9 (25)
Pyrexia	22.5 (25)	22.0 (24)
Hypoalbuminaemia	19.8 (22)	18.3 (20)
Anaemia	13.5 (15)	18.3 (20)
Cerebral vasoconstriction	43.2 (48)	16.5 (18)
Hypokalaemia	16.2 (18)	16.5 (18)
Insomnia	13.5 (15)	15.6 (17)
Pleural effusion	5.4 (6)	15.6 (17)
Cerebral infarction	20.7 (23)	14.7 (16)
Headache	17.1 (19)	13.8 (15)
Hydrocephalus	21.6 (24)	11.0 (12)
Vomiting	5.4 (6)	11.0 (12)
Liver function test abnormal	8.1 (9)	10.1 (11)
Pulmonary oedema	3.6 (4)	10.1 (11)
Liver function test increased	14.4 (16)	7.3 (8)

Incidence % (number of subjects with events)

The incidence of adverse events leading to death within 12 weeks after aSAH onset was 1.8% (2 of 111 subjects; subarachnoid haemorrhage and acute respiratory failure in 1 subject each) in the placebo group and 0.9% (1 of 109 subjects; subarachnoid haemorrhage) in the clazosentan group. These events were considered to be unrelated to the study drug.

The incidence of serious adverse events that occurred between the start of study drug administration and 30 days after the completion (discontinuation) of administration was 22.5% (25 of 111) of subjects in the placebo group and 19.3% (21 of 109) of subjects in the clazosentan group. Serious adverse events observed in more than 1 subject in either group were hydrocephalus (7.2% in the placebo group, 2.8% in the clazosentan group), vascular pseudoaneurysm (0%, 2.8%), brain oedema (2.7%, 1.8%), cerebral infarction (4.5%, 1.8%), cerebral vasoconstriction (1.8%, 1.8%), and subarachnoid haemorrhage (1.8%, 0.9%). All events were considered to be unrelated to the study drug, except brain oedema in 1 subject in the placebo group and pulmonary oedema, pneumonia, and brain oedema in 1 subject each in the clazosentan group.

The incidence of adverse events leading to discontinuation of the study drug was 12.6% (14 of 111) of subjects in the placebo group and 13.8% (15 of 109) of subjects in the clazosentan group. Adverse events leading to discontinuation of the study drug in more than 1 subject in either group were cerebral vasoconstriction (7.2% in the placebo group, 5.5% in the clazosentan group), delayed ischaemic neurological deficit (2.7%, 3.7%), pulmonary oedema (0%, 3.7%), cerebral infarction (0.9%, 1.8%),

vascular pseudoaneurysm (0%, 1.8%), and brain oedema (1.8%, 0.9%). All events were considered to be unrelated to the study drug, except pulmonary oedema in 4 subjects in the clazosentan group.

7.2.2 Japanese phase III study (Study AC-054-305; CTD 5.3.5.1.6; Study period, [redacted] to [redacted])

A randomized, double-blind, parallel-group study was conducted to investigate the effect of clazosentan in preventing M/M events in patients who had undergone coiling for aSAH (target sample size, 220 subjects) at 46 study sites in Japan. The initial target sample size was 160[15)] and, when 160 subjects were enrolled, the incidence of M/M events was reviewed under blinded conditions in 98 subjects who had completed the assessment by the imaging review committee, the event assessment committee, and the hematoma mass subcommittee. Results showed that the incidence of M/M events was 10.2%, which was lower than the level assumed at the study planning (28%); this suggested that the statistical power was as low as approximately 38%. Accordingly, the target sample size was re-estimated. Thus, by assuming the incidence of M/M events to be 14.2% in the placebo group and 6.2% in the clazosentan group, at least 144 to 219 subjects per group were estimated to be required for detecting the treatment effect (relative risk reduction rate) of approximately 43% at the statistical power of 80% to 90%. However, because of feasibility issues, the target sample size was determined to be 110 per group[16)] as was the case in Study 306.

The intravenous administration of placebo or clazosentan was started as soon as possible within 48 hours after aSAH onset, and was continued until Day 14 after the onset (for 15 days at the longest). The content of 2 vials (each vial was filled with a 6 mL of solution containing clazosentan 150 mg [25 mg/mL]) was diluted with 500 mL of physiological saline. The diluted solution was administered at the speed of 17 mL/h (10 mg/h of clazosentan). Rescue therapies and prohibited concomitant drugs during the study drug administration period up to Week 6 after aSAH onset were the same as those stipulated in Study 306.

The main inclusion and exclusion criteria were the same as those in Study 306 except operative method. The study used dynamic allocation procedure (allocation ratio 1:1) according to the WFNS grade (I, II, III, and IV).

Of 221 randomized subjects (111 in the placebo group, 110 in the clazosentan group), 220 subjects (111 in the placebo group, 109 in the clazosentan group) were included in the FAS and in the safety analysis set (the remaining 1 subject who did not receive the study drug was excluded). The FAS was handled as the primary efficacy analysis set. Within 12 weeks after aSAH onset, study discontinuation occurred in 12.6% (14 of 111) of subjects in the placebo group and in 10.0% (11 of 110) of subjects in the clazosentan group. Main reasons for the discontinuation were adverse events in 11 subjects (7 in

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15) From the results of foreign phase III studies (Studies AC-054-301 and AC-054-302), the incidence of M/M events was assumed not to differ between after clipping and after coiling. With reference to the incidence of cerebrovascular spasm-associated M/M events except "initiation of rescue therapy" in the Japanese and South Korean joint phase II study (Study AC-054-202), the incidence of M/M events in the placebo group and the clazosentan group was assumed to be 39% and 17%, respectively, and the required sample size was estimated to be 77 subjects per group to detect a statistically significant between-group difference by Cochran-Mantel-Haenszel test (two-sided significance level of 5%, statistical power 0.9). Under these assumptions, the statistical power of the hypothesis test based on the hierarchical closed testing procedure was 0.90 for the primary endpoint (1) and 0.87 for the primary endpoint (2). By assuming the number of subjects excluded from FAS to be 3 per group, the target sample size was determined to be 80 per group.

16) Under these assumptions, the statistical power of the hypothesis test based on the hierarchical closed testing procedure was 50% for the primary endpoint (1) and 40% for the primary endpoint (2).

the placebo group, 4 in the clazosentan group), use of prohibited concomitant drugs in 9 subjects (6, 3), and extensive brain oedema or severe pulmonary oedema in 4 subjects (0, 4). The duration of the study drug administration (median [min., max.]) was 12.12 [3.3, 13.6] days in the placebo group and 12.50 [0.9, 13.3] days in the clazosentan group.

Presence (≥1 site) or absence of moderate or severe cerebrovascular spasm, occurrence of new cerebral infarction, and the relationship between cerebrovascular spasm and the new cerebral infarction were evaluated based on DSA and CT images by the central imaging review committee under blinded conditions. Presence or absence of DIND, appropriateness of starting rescue therapy, and the relationship between cerebrovascular spasm and death, new cerebral infarction (when DSA or CT image was unavailable), DIND, or initiation of rescue therapy was evaluated by the event assessment committee under blinded conditions.

Efficacy was evaluated based on 2 primary endpoints:

Primary endpoint (1): Cerebrovascular spasm-associated M/M events occurring between the start of study drug administration and Week 6 after aSAH onset.

Primary endpoint (2): All-cause M/M events occurring between the start of study drug administration and Week 6 after aSAH onset.

Table 28 shows the results of the primary endpoints and their components. The incidence of cerebrovascular spasm-associated M/M events, the primary endpoint (1), was significantly lower in the clazosentan group than in the placebo group. Since a significant between-group difference was observed in the primary endpoint (1), the results of the primary endpoint (2) were analyzed based on the hierarchical closed testing procedure. No significant difference was observed in the incidence of all-cause M/M events between the clazosentan and placebo groups.

Table 28. Incidence of M/M events within 6 weeks after aSAH onset (FAS)

	Placebo (n = 111)	Clazosentan (n = 109)	Between-group difference [exact 95% CI]	*P* value[a]
Primary endpoint (1)				
Cerebrovascular spasm-associated M/M events	28.8 (32/111)	13.6 (14/103[b])	−15.2 [−28.3, -1.8]	0.0055
All-cause deaths	2.7 (3/111)	1.8 (2/109)		
Cerebrovascular spasm-associated new cerebral infarction	21.6 (24/111)	12.4 (13/105[b])		
Cerebrovascular spasm-associated DIND	18.0 (20/111)	7.5 (8/107[b])		
Primary endpoint (2)				
All-cause M/M events	41.4 (46/111)	33.0 (34/103)	−8.4 [−21.7, 5.0]	0.1871
All-cause deaths	2.7 (3/111)	1.8 (2/109)		
New cerebral infarction	31.5 (35/111)	26.7 (28/105[b])		
DIND	23.4 (26/111)	15.9 (17/107[b])		

Incidence % (number of subjects with events/number of subjects analyzed)

a Cochran-Mantel-Haenszel test with the covariate of WFNS grade (4 grades) before coiling (two-sided significance level of 5%). First, the primary endpoint (1) was to be subjected to test according to the hierarchical closed testing procedure and, only if a between-group difference was observed, the primary endpoint (2) was to be subjected to the test.

b The analysis of the presence/absence of cerebrovascular spasm and new cerebral infarction excluded subjects who did not receive DSA or CT (including unspecified test) by Week 6 and subjects unevaluable for DIND until Week 6.

The incidence of moderate or severe cerebrovascular spasm within 14 days after aSAH onset, the secondary endpoint, was 49.5% (55 of 111) of subjects in the placebo group and 28.4% (31 of 109) of subjects in the clazosentan group.

Rescue therapy that could be used in combination with the study drug was performed in 22.5% (25 of 111) of subjects in the placebo group and 11.9% (13 of 109) of subjects in the clazosentan group. Rescue therapy requiring discontinuation of the study drug was performed in 9.9% (11 of 111) of subjects in the placebo group and 2.8% (3 of 109) of subjects in the clazosentan group.

The incidence of adverse events that occurred from the start of study drug administration up to 30 days after the completion (discontinuation) of the administration was 92.8% (103 of 111) of subjects in the placebo group and 89.9% (98 of 109) of subjects in the clazosentan group. Table 29 shows adverse events with an incidence of ≥10% in either group.

Table 29. Adverse events with an incidence of ≥10% in either group (safety analysis set)

MedDRA PT	Placebo (n = 111)	Clazosentan (n = 109)
Constipation	36.9 (41)	35.8 (39)
Hyponatraemia	19.8 (22)	22.9 (25)
Pleural effusion	1.8 (2)	17.4 (19)
Hypoalbuminaemia	5.4 (6)	16.5 (18)
Pyrexia	23.4 (26)	16.5 (18)
Cerebral infarction	15.3 (17)	15.6 (17)
Cerebral vasoconstriction	32.4 (36)	15.6 (17)
Delayed ischaemic neurological deficit	24.3 (27)	15.6 (17)
Anaemia	5.4 (6)	14.7 (16)
Pulmonary oedema	5.4 (6)	13.8 (15)
Hypokalaemia	11.7 (13)	12.8 (14)
Headache	16.2 (18)	11.9 (13)
Hydrocephalus	10.8 (12)	9.2 (10)
Insomnia	12.6 (14)	8.3 (9)

Incidence % (number of subjects with events)

The incidence of adverse events leading to death within 12 weeks after aSAH onset was 2.7% (3 of 111 subjects; cerebral infarction/cerebrovascular spasm, cerebral infarction, and subarachnoid haemorrhage in 1 subject each) in the placebo group and 1.8% (2 of 109 subjects; blood pressure decreased and cerebral infarction in 1 subject each) in the clazosentan group. All events were considered to be unrelated to the study drug.

The incidence of serious adverse events that occurred between the start of study drug administration and 30 days after the completion (discontinuation) of administration was 18.9% (21 of 111) of subjects in the placebo group and 15.6% (17 of 109) of subjects in the clazosentan group. Serious adverse events observed in more than 1 subject in either group were cerebral infarction (2.7% in the placebo group, 3.7% in the clazosentan group), vitreous haemorrhage (0.9%, 2.8%), brain oedema (0%, 1.8%), urinary tract infection (0%, 1.8%), intracranial aneurysm (1.8%, 0.9%), cerebral vasoconstriction (5.4%, 0%), hydrocephalus (4.5%, 0%), and subarachnoid haemorrhage (2.7%, 0%). All events were considered to be unrelated to the study drug, except cerebrovascular spasm in 1 subject in the placebo group and haemorrhage intracranial in 1 subject in the clazosentan group.

The incidence of adverse events leading to discontinuation of the study drug was 10.8% (12 of 111) of subjects in the placebo group and 9.2% (10 of 109) of subjects in the clazosentan group. Adverse events leading to discontinuation of the study drug in more than 1 subject in either group were brain oedema (0% in the placebo group, 1.8% in the clazosentan group), cerebral infarction (2.7%, 1.8%), cerebrovascular spasm (6.3%, 1.8%), pleural effusion (0%, 1.8%), delayed ischaemic neurological deficit (3.6%, 0%), and subarachnoid haemorrhage (1.8%, 0%). All events were considered to be unrelated to the study drug, except pleural effusion in 2 subjects in the clazosentan group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of clazosentan

The applicant's explanation about the clinical positioning of clazosentan:

SAH is a collective term for haemorrhage into subarachnoid space within cranium (cavity filled with cerebrospinal fluid between arachnoid mater and brain surface). Most of SAH is caused by rupture of cerebral aneurysm (aSAH), which accounts for 85% of all SAH cases (Japanese Guidelines for the Management of Stroke 2021). Cerebrovascular spasm, a reversible constriction of the major cerebral artery, occurs at the frequency of 40% to 70% between 4 and 14 days after aSAH onset (*CNS Neurosci Ther.* 2019;25:1096-112), and 17% to 40% of patients who have experienced cerebrovascular spasm develop DIND and half of them progress to cerebral infarction (*Neurosurg Rev*. 2007;30:22-30). Cerebrovascular spasm is related to the development and poor prognosis of cerebral infarction and to poor functional outcome (*Stroke.* 2011;42:919-23, *Nat Rev Neurol*. 2014;42:635-57). Prevention and treatment of cerebrovascular spasm is thus an important issue for improving prognosis in patients with aSAH.

Japanese Guidelines for the Management of Stroke 2021 state that preventing rebleeding is extremely important in the treatment of ruptured cerebral aneurysm, and recommends surgical intervention by craniotomy (clipping) or endovascular treatment (coiling) depending on the patient conditions and the site, shape, and size of ruptured cerebral aneurysm (Level A recommendation, "highly recommended"). As a systemic drug therapy for cerebrovascular spasm after surgery to prevent rebleeding, intravenous administration of fasudil hydrochloride hydrate or ozagrel sodium is recommended (Level B recommendation, "reasonable"). However, moderate or severe cerebrovascular spasm may occur even in patients receiving these drugs, and the conventional drugs have safety problems such as bleeding. Thus, there are unmet needs for the treatment of aSAH.

Although the exact mechanism of the development of cerebrovascular spasm is still unclear, it is supposed that, after aSAH onset, ET production is induced by oxidized hemoglobin and ET is released from erythrocytes, resulting in an increase in the concentration of ET, a potent and lasting vasoconstrictor, in the cerebrospinal fluid, thereby causing cerebrovascular spasm (*Stroke*. 1994;25:904-8, *Eur J Pharmacol*. 1994;271:131-9, etc.). Clazosentan, an ERA, is expected to suppress ET-mediated cerebrovascular spasm after aSAH, and may serve as a novel drug with a different mechanism of action from that of approved drugs used for the suppression of cerebrovascular spasm after aSAH.

In the clinical studies of clazosentan, the drug not only prevented cerebrovascular spasm but also reduced the percentage of subjects who had M/M events, regardless of the method of treatment after aSAH onset (clipping or coiling). As for safety, the incidence of adverse events (e.g., bleeding, a risk with approved drugs) in the clazosentan group was not significantly higher than that in the placebo group.

Based on the above, clazosentan is considered to be a drug that should be recommended for patients early after surgery for aSAH, along with fasudil hydrochloride hydrate and ozagrel sodium.

PMDA's view:
Preventing cerebrovascular spasm-associated cerebral infarction after aSAH is an important clinical issue, and Japanese Guidelines for the Management of Stroke 2021 propose various treatment options, but there are still unmet needs as explained by the applicant. It is meaningful to make clazosentan available in clinical practice as a novel treatment option for the prevention of cerebrovascular spasm and associated cerebral infarction after surgical treatment of aSAH, for the following reasons:

(a) The Japanese phase III studies demonstrated the clinically significant efficacy and acceptable safety of clazosentan.
(b) Clazosentan acts as an endothelin receptor antagonist, a novel mechanism of action in the treatment of aSAH, and therefore has efficacy and safety profiles different from those of conventional drugs [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"].

In the clinical use of clazosentan, however, it is necessary to (a) promote the understanding of the risks of clazosentan different from those of approved drugs, including fluid retention such as pleural effusion and pulmonary oedema, (b) provide information on the characteristics of clazosentan so that a drug suitable for each patient is selected from among multiple choices including clazosentan, and (c) issue appropriate cautionary statements. Appropriateness of the above conclusion by PMDA will be determined, also taking account of comments raised in the Expert Discussion.

7.R.2 Efficacy

7.R.2.1 Target patients and primary endpoints

The applicant conducted 2 Japanese phase III studies, Study AC-054-306 (Study 306) and Study AC-054-305 (Study 305), using 2 primary endpoints of (1) cerebrovascular spasm-related M/M events and (2) all-cause M/M events.

The applicant' rationale for the studies:
Study patients
Since ruptured cerebral aneurysm is treated by either of 2 methods, clipping and coiling, the applicant considered that clazosentan should be developed as a postoperative treatment drug for both methods. At the time of the study planning, it was unknown whether the same efficacy and safety results could be obtained in both patients undergoing clipping and those undergoing coiling. Two separate studies were therefore planned to evaluate the efficacy of clazosentan after clipping and coiling independently.

Primary endpoints

It was considered essential to evaluate clinical events that occur subsequent to cerebrovascular spasm and affect prognosis. Therefore, occurrence of cerebrovascular spasm-associated M/M events was used at the first step of the hierarchical closed testing procedure. In both clinical studies, the target sample size was determined based on the incidence of cerebrovascular spasm-associated M/M events, the parameter used as the exploratory endpoint in Study AC-054-202. The primary objective of both studies was to achieve the primary endpoint (1). Further, because bleeding occurs at various sites in aSAH and may be caused by the vasospasm of microvessels undetectable by DSA, primary endpoint (2) was used as the second step of the hierarchical closed testing procedure, in order to confirm the efficacy in preventing M/M events regardless of their association with cerebrovascular spasm, thereby to further confirm the appropriateness of the assessment of primary endpoint (1).

PMDA's view:
The following clinical study strategies adopted by the applicant were acceptable:

- Based on the information available at the timing of the study planning, the clinical studies enrolled patients who had undergone clipping or coiling, the hemostatic procedures commonly performed after aSAH.
- Two separate confirmatory studies were conducted: one study enrolled patients after clipping and the other study enrolled patients after coiling.

Using primary endpoints (1) and (2) in both studies were appropriate because both endpoints are clinically important events related to prognosis after surgery for aSAH. Primary endpoint (1) (cerebrovascular spasm-associated M/M events) was used at the first step of the hierarchical closed testing procedure because it was considered to be related to the mechanism of action of clazosentan (competition for binding to endothelin receptor); this was also appropriate.

7.R.2.2 Results of efficacy evaluation

The applicant's explanation about the efficacy of clazosentan:
As shown in Tables 26 and 28, results of Studies 306 and 305 demonstrated that the incidence of cerebrovascular spasm-associated M/M events, primary endpoint (1), was statistically significantly lower in the clazosentan group than in the placebo group among patients with aSAH, regardless of whether they had undergone clipping or coiling. Also, the incidences of all-cause deaths, cerebrovascular spasm-associated new cerebral infarction, and cerebrovascular spasm-associated DIND (these are the components of primary endpoint (1)) were lower in the clazosentan group than in the placebo group. Furthermore, the incidence of moderate or severe cerebrovascular spasm within 14 days after aSAH onset, the secondary endpoint, was also lower in the clazosentan group than in the placebo group in both clinical studies.

The incidence of all-cause M/M events, primary endpoint (2), did not significantly differ between the clazosentan and placebo groups either in Study 306 or 305. This was probably because the insufficient sample size determined at re-estimation (the sample size was reduced from the re-estimated number for feasibility purposes) could not demonstrate the superiority of clazosentan to placebo in this endpoint. Therefore, the proposed indication of clazosentan clearly states that the expected efficacy of clazosentan is prevention of cerebrovascular spasm and cerebrovascular spasm-associated cerebral infarction and cerebral ischemic episodes after treatment of aSAH.

Clazosentan was developed first in foreign countries, and Study AC-054-301[5)] in patients who underwent clipping for aSAH and Study AC-054-302[6)] in patients who underwent coiling for aSAH were conducted. In Study AC-054-301, no significant difference was detected between the placebo group and the clazosentan 5 mg/h group in the incidence of cerebrovascular spasm-associated M/M events up to Week 6 after aSAH onset, the primary endpoint. In response to this result, the then-ongoing Study AC-054-302 was terminated early. In Study AC-054-301 (which was conducted based on the results of the foreign Study AC-054-201[7)]), clazosentan was administered at a dose of 5 mg/h to patients who had diffuse hematoma (major axis ≥20 mm or extending to both hemispheres). The possible reasons Study AC-054-301 failed to demonstrate the efficacy are as follows:

(a) Hypotension, which occurred more frequently in the clazosentan group, and respiratory adverse events may have affected efficacy evaluation.
(b) Oral nimodipine (unapproved in Japan) was co-administered to approximately four fifth of patients; this may have interfered with detection of the efficacy of clazosentan.
(c) Higher frequency of rescue therapy given to subjects in the placebo group may have obscured the between-group difference of the efficacy.
(d) Death for reasons other than cerebral ischaemia occurred frequently in the clazosentan group.

Also, the dose of clazosentan 5 mg/h was probably lower than the optimal dose, judging from that the incidence of M/M events in the clazosentan 15 mg/h group tended to be lower, although this finding was obtained at the discontinuation of Study AC-054-302. Currently, a foreign phase III study (Study ID-054-304[17)]) is ongoing to investigate the efficacy and safety of clazosentan 15 mg/h versus placebo in patients who had undergone clipping or coiling for aSAH. Study AC-054-301 was conducted in "patients with diffuse hematoma (major axis ≥20 mm or extending to both hemispheres)" and Study AC-054-302 in "patients with thick hematoma (minor axis ≥4 mm)," because subarachnoidal blood volume is correlated with occurrence of cerebrovascular spasm, functional deterioration due to DIND, cerebral infarction, and poor clinical outcome. In both studies, the incidence of M/M events in the placebo group was higher in subjects with "diffuse and thick (major axis 20 mm or extending to both hemispheres, and minor axis ≥4 mm)" than in other subjects. In Study AC-054-302, subjects receiving clazosentan 15 mg/h in the "diffuse thick hematoma" population showed a decreasing trend in DIND and in relative risk of rescue therapy. Based on the above, Study ID-054-304 enrolled patients with "diffuse and thick hematoma" (>4 mm-thick diffuse blood clot containing 3 or more basal layers). The Japanese phase III studies (Studies 306 and 305), the pivotal studies for the present application, evaluated the 10 mg/h dose based on the results of Study AC-054-202 [see Section "7.R.5 Dosage and administration"], and adopted the same enrollment criteria as those in Studies AC-054-301 and AC-054-302, except the following:

(a) Studies 306 and 305 enrolled patients with Fisher grade 3 (localized blood clot or blood ≥1 mm thick in the layer perpendicular to CT cross section) because they are at high risk for cerebrovascular spasm.

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17) A placebo-controlled, parallel-group, double-blind study to investigate the efficacy and safety in patients who underwent clipping or coiling for aSAH (phase III study). The primary endpoint was worsening of clinical symptoms due to delayed cerebral ischemia within 14 days after the start of study drug administration, assessed by mGCS or abbreviated National Institutes of Health Stroke Scale (aNIHSS). The study enrolled patients with WFNS grade I to IV who met either of the following criteria: (a) Patients with diffuse thick hematoma who were able to start receiving the study drug within 96 hours after the onset of aSAH or (b) patients without diffuse thick hematoma who experienced moderate to severe cerebrovascular spasm within 14 days after the onset of aSAH and were able to start receiving the study drug within 24 hours after the onset of cerebrovascular spasm. The target sample size was 400 patients (assigned at a ratio of 1:1 to receive placebo or clazosentan 15 mg/h). (Study period, ongoing since June 2021)

(b) In Studies 306 and 305, the study drug administration was started within 48 hours after aSAH onset.

Studies 306 and 305 demonstrated the efficacy of clazosentan as described above.

Table 30 shows patient characteristics in Study 306 in patients who underwent clipping for aSAH and in Study 305 in patients who underwent coiling for aSAH. There were no significant differences between the 2 studies in age, sex, WFNS grade, size of hematoma, etc. of patients. However, as anticipated, the time required for clipping was longer than that for coiling, and the most frequent site of the ruptured cerebral aneurysm was middle cerebral artery in patients who underwent clipping and internal carotid artery in patients who underwent coiling (among internal carotid artery, anterior cerebral artery, middle cerebral artery, etc.). According to the results of the subpopulation analysis classified by the site of ruptured cerebral aneurysm (Table 31), in both Study 306 and Study 305, (a) the incidence of M/M events tended to be higher in patients receiving placebo in the subpopulation of "middle cerebral artery (ruptured site)," and (b) the incidence of M/M events tended to be lower in patients receiving clazosentan than in those receiving placebo in all subpopulations. These findings suggest that the difference in these patient characteristics between those undergoing clipping and those undergoing coiling is unlikely to affect the evaluation of efficacy. The efficacy of clazosentan was demonstrated in both Studies 306 and 305, and the 2 studies had no clear difference in patient characteristics affecting the efficacy; thus clazosentan has efficacy regardless of the type of surgery.

Table 30. Patient characteristics (safety analysis set)

		Study 306		Study 305	
		Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Age (years)		59.6 ± 9.5	57.1 ± 11.5	57.6 ± 10.4	56.8 ± 10.3
Sex	Male	40.5 (45)	32.1 (35)	26.1 (29)	33.0 (36)
	Female	59.5 (66)	67.9 (74)	73.9 (82)	67.0 (73)
WFNS grade (at screening)	I/II	74.8 (83)	75.2 (82)	73.9 (82)	74.3 (81)
	III/IV	25.2 (28)	24.8 (27)	26.1 (29)	25.7 (28)
Size of hematoma	Diffuse and thick	60.4 (67)	46.8 (51)	49.5 (55)	45.9 (50)
	Other	39.6 (44)	53.2 (58)	50.5 (56)	54.1 (59)
Site of ruptured aneurysm	Anterior cerebral artery	36.9 (41)	33.0 (36)	38.7 (43)	33.9 (37)
	Internal carotid artery	22.5 (25)	28.4 (31)	45.9 (51)	44.0 (48)
	Middle cerebral artery	39.6 (44)	35.8 (39)	6.3 (7)	12.8 (14)
	Posterior cerebral artery	0 (0)	0.9 (1)	0 (0)	2.8 (3)
	Vertebral artery	0 (0)	1.8 (2)	4.5 (5)	1.8 (2)
	Basilar artery	0 (0)	0 (0)	5.4 (6)	5.5 (6)
Time required for surgery		5.38 ± 1.74	5.38 ± 1.88	2.46 ± 1.16	2.39 ± 1.04

Table 31. Incidence of M/M events by site of ruptured aneurysm (FAS)

	Study 306		Study 305	
	Placebo	Clazosentan	Placebo	Clazosentan
Anterior cerebral artery	43.9 (18/41)	25.7 (9/35)	32.6 (14/43)	15.2 (5/33)
Internal carotid artery	29.2 (7/24)	10.3 (3/29)	27.5 (14/51)	19.1 (9/47)
Middle cerebral artery	40.0 (16/40)	13.2 (5/38)	42.9 (3/7)	7.1 (1/14)

Incidence % (number of subjects with events/number of subjects analyzed)

In Studies 306 and 305, the target sample size was changed as a result of a blinded review conducted during the study. Therefore, PMDA asked the applicant to compare the patient characteristics and the incidence of events between before and after the additional patient enrollment and to explain the effect of the increase in sample size under the blinded review on the evaluation of the efficacy in each study.

The applicant's explanation:

Table 32 shows the characteristics of patients enrolled in Studies 306 and 305 before and after the increase in the sample size (cut-off date November 30, 2018) and the incidence of cerebrovascular spasm-associated M/M events observed before and after the blinded review. There was no significant difference in the characteristics of patients enrolled before and after the sample size increase. The incidence of cerebrovascular spasm-associated M/M events was higher after the blinded review than before the blinded review, but the incidence of M/M events was lower in the clazosentan group than in the placebo group at all time points evaluated, showing no change in the relation between the clazosentan and placebo groups. These results mean that neither the blinded review nor the increase of the sample size significantly affected the efficacy evaluation. It is therefore appropriate to evaluate the combined results obtained before and after the blinded review.

Table 32. Patient characteristics before and after sample size increase and incidence of cerebrovascular spasm-associated M/M events before and after blinded review (FAS)

		Study 306				Study 305			
		Before the increase in target sample size (patient characteristics)/ before blinded review (M/M events)		After the increase in target sample size (patient characteristics)/ after blinded review (M/M events)		Before the increase in target sample size (patient characteristics)/ before blinded review (M/M events)		After the increase in target sample size (patient characteristics)/ after blinded review (M/M events)	
		Placebo (n = 80)	Clazosentan (n = 82)	Placebo (n = 31)	Clazosentan (n = 27)	Placebo (n = 80)	Clazosentan (n = 79)	Placebo (n = 31)	Clazosentan (n = 30)
Age (years)		59.5 ± 9.6	58.0 ± 11.8	59.7 ± 9.6	54.7 ± 10.5	58.6 ± 10.0	57.3 ± 10.6	55.1 ± 11.1	55.4 ± 9.8
Sex	Male	41.3 (33)	34.1 (28)	38.7 (12)	25.9 (7)	25.0 (20)	34.2 (27)	29.0 (9)	30.0 (9)
	Female	58.8 (47)	65.9 (54)	61.3 (19)	74.1 (20)	75.0 (60)	65.8 (52)	71.0 (22)	70.0 (21)
Weight (kg)		61.0 ± 11.9	57.6 ± 12.1	63.1 ± 16.3	57.6 ± 11.1	58.3 ± 12.3	59.7 ± 11.8	61.0 ± 12.9	62.3 ± 14.4
WFNS grade	I/II	76.3 (61)	76.8 (63)	71.0 (22)	70.4 (19)	76.3 (61)	75.9 (60)	67.7 (21)	70.0 (21)
	III/IV	23.8 (19)	23.2 (19)	29.0 (9)	29.6 (8)	23.8 (19)	24.1 (19)	32.3 (10)	30.0 (9)
Hematoma size	Diffuse and thick	60.0 (48)	45.1 (37)	61.3 (19)	51.9 (14)	45.0 (36)	46.8 (37)	61.3 (19)	43.3 (13)
	Other	40.0 (32)	54.9 (45)	38.7 (12)	48.1 (13)	55.0 (44)	53.2 (42)	38.7 (12)	53.3 (16)
Cerebrovascular spasm-associated M/M events[a]		42.1 (16/38)	10.3 (4/39)	38.2 (26/68)	19.7 (13/66)	23.4 (11/47)	8.0 (4/50)	32.8 (21/64)	18.9 (10/53)

a Subjects who completed event evaluation were subjected to analysis in blinded review.

PMDA's view:

In the Japanese phase III studies, the pivotal studies in the present application, the sample size was re-adjusted according to the results of the blinded review. In Studies 306 and 305, (a) patient characteristics and (b) the between-group difference in the incidence of cerebrovascular spasm-associated M/M events did not change significantly before and after the sample size increase or the blinded review. PMDA therefore concluded that it was acceptable to evaluate the combined results obtained before and after blinded review, and evaluated the results of each study (see below for detains).

(a) Patients who underwent clipping for aSAH

In Study 306, the incidence of cerebrovascular spasm-associated M/M events, the primary efficacy endpoint (1), was significantly lower in the clazosentan group than in the placebo group, and the relative risk reduction rate (clazosentan/placebo) was 0.59, which was not significantly different from the level pre-estimated based on the results of the Japanese and South Korean joint phase II study of clazosentan (Study AC-054-202). Also, compared with the placebo group, the clazosentan group had

lower incidences of all-cause deaths, cerebrovascular spasm-associated new cerebral infarction, and cerebrovascular spasm-associated DIND (all are the components of the primary endpoints) and moderate and severe cerebrovascular spasm (the secondary endpoint). Based on the above, PMDA considers that clazosentan has shown clinically significant efficacy in preventing clinical events related to cerebrovascular spasm-associated prognosis. No significant difference in primary endpoint (2) was observed between the clazosentan and placebo groups, but the point estimates of its incidence tended to be lower in the clazosentan group than in the placebo group; this supports the results of primary endpoint (1).

(b) Patients who underwent coiling for aSAH

In Study 305, the incidence of cerebrovascular spasm-associated M/M events, the primary efficacy endpoint (1), was significantly lower in the clazosentan group than in the placebo group. The incidences of all-cause deaths, cerebrovascular spasm-associated new cerebral infarction, cerebrovascular spasm-associated DIND (all are the components of the primary endpoint (1)) and moderate and severe cerebrovascular spasm (the secondary endpoint) were lower in the clazosentan group than in the placebo group. Prior to starting the Japanese phase III studies, there was no information available on the incidence of M/M events or the recommended dose of clazosentan in Japanese patients who underwent coiling for aSAH. Therefore, the target sample size was determined based on (a) the incidence of cerebrovascular spasm-associated M/M events and (b) the relative risk reduction rate in Study AC-054-202 in patients undergoing clipping. Although the incidence of cerebrovascular spasm-associated M/M events in the placebo group was lower than expected, the relative risk reduction rate in the clazosentan group compared with the placebo group (0.53) was close to the pre-assumed rate and did not significantly differ from the result of Study 306. Based on the above, PMDA considers that clazosentan demonstrated clinically significant efficacy. Meanwhile, no significant difference was observed in the results of the primary endpoint (2) between the clazosentan and placebo groups, but the point estimates of the incidence tended to be lower in the clazosentan group than in the placebo group; this finding supported the results of the primary endpoint (1).

The foreign phase III studies (Studies AC-054-301 and AC-054-302) conducted ahead of the Japanese phase III studies, could not demonstrate the efficacy of clazosentan. However, this does not affect the evaluation of the Japanese phase III studies, taking into account the following points:

(a) The applicant's explanation that the insufficient dose of clazosentan was the main reason why the foreign phase III studies could not demonstrate the efficacy [see Section "7.R.5 Dosage and administration"].
(b) The difference in the study design between Japanese and foreign phase III studies.
(c) The results of the above Japanese phase III studies.

Thus, PMDA concludes that clazosentan has demonstrated clinically significant efficacy for the prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes.

7.R.2.3 Factors affecting efficacy

The applicant's explanation about factors affecting the efficacy of clazosentan:

Table 33 shows the incidence of cerebrovascular spasm-associated M/M events, classified by hematoma size and SAH severity (WFNS grade of neurological symptoms before surgery) in Studies 306 and 305.

Table 33. Incidence of cerebrovascular spasm-associated M/M events, classified by hematoma size and WFNS grade (FAS)

		Study 306		Study 305	
		Placebo	Clazosentan	Placebo	Clazosentan
Hematoma size[a]	No hematoma	0 (0/2)	0 (0/5)	16.7 (1/6)	0 (0/6)
	Localized and thin	28.6 (4/14)	0 (0/15)	13.3 (2/15)	0 (0/15)
	Localized and thick	28.6 (2/7)	0 (0/15)	16.7 (2/12)	0 (0/5)
	Diffuse and thin	15.8 (3/19)	13.6 (3/22)	26.1 (6/23)	6.5 (2/31)
	Diffuse and thick	51.6 (33/64)	29.2 (14/48)	38.2 (22/55)	26.1 (12/46)
WFNS grade	I or II	35.0 (28/80)	11.3 (9/80)	23.2 (19/82)	10.4 (8/77)
	III or IV	53.8 (14/26)	32.0 (8/25)	44.8 (13/29)	23.1 (6/26)

Incidence % (number of subjects with events/number of subjects analyzed)

a Classified by the hemorrhage volume assessment committee under blinded conditions according to 5 categories:
No hematoma, minor axis <1 mm;
Localized and thin, major axis <20 mm, minor axis ≥1 mm and <4 mm;
Localized and thick, major axis <20 mm, minor axis ≥4 mm;
Diffuse and thin, major axis ≥20 mm or spreading to both hemispheres, minor axis ≥1 mm and <4 mm; and
Diffuse and thick, major axis ≥20 mm or extending to both hemispheres, minor axis ≥4 mm).

Studies 306 and 305 enrolled patients at high risk of cerebrovascular spasm, i.e., patients with Fisher grade 3 (localized blood clot or blood ≥1 mm thick in the layer perpendicular to CT cross section). Results of subpopulation analysis showed a tendency of a higher incidence of M/M events in subjects with a more diffuse and thicker hematoma, whereas the incidence of M/M events was lower in the clazosentan group than in the placebo group in all subpopulations. This suggests that clazosentan is effective regardless of the size of hematoma. For the reasons shown below, even patients with small hematoma should receive therapeutic intervention to prevent cerebrovascular spasm, and the clinical study results suggest that patients with Fisher grade 1 or 2 are eligible for receiving treatment with clazosentan:

- The severity of delayed cerebrovascular spasm is considered to be correlated with the volume of perivascular hematoma within subarachnoid space (Japanese Guidelines for the Management of Stroke 2015 [supplementary edition 2019]), but cerebrovascular spasm occurs in a certain percentage of patients with Fisher grade 1 (no blood observed within subarachnoid space) or 2 (diffuse or thin blood with <1 mm thickness in all layers perpendicular to CT cross section [interhemispheric fissure, insular cistern, and ambient cistern]) (Japan Stroke Data Bank, 2021).
- Once cerebrovascular spasm has occurred, the risk of developing cerebral infarction and DIND (which are related to prognosis) is similar regardless of the hematoma size.

As for aSAH severity, Studies 306 and 305 enrolled patients with WFNS grade I to IV before and after surgery. In the studies, the incidence of M/M events tended to be higher in the population of pre-operative WFNS grade III/IV than in the population of pre-operative WFNS grade I/II. In all subpopulations, the incidence of M/M events was lower in patients receiving clazosentan than in those receiving placebo. Patients with WFNS grade V who had the severest disease were excluded from the clinical studies because their poor conditions may preclude neurological assessment. According to

Japanese Guidelines for the Management of Stroke 2021, WFNS grade V is not eligible for surgery to prevent rebleeding as a general rule. However, the Guidelines also state that (a) patients may be eligible for the rebleeding-preventive surgery if impairment of consciousness is due to increased intracranial pressure caused by intracerebral hematoma or by acute hydrocephalus and surgery is expected to improve the symptoms, and that (b) even severe cases (WFNS grade V or IV) may be eligible for acute phase surgery in young patients and patients with middle cerebral artery aneurysm. Thus, in clinical settings, probably there are patients with WFNS grade V who undergo surgery. In clinical studies, the efficacy of clazosentan did not tend to decrease with increased severity in patients with WFNS grade from I to IV, suggesting that clazosentan is effective in patients with WFNS grade V as well. It is important to prevent cerebrovascular spasm and cerebrovascular spasm-associated events even in patients with WFNS grade V. Therefore in clinical settings, patients with WFNS grade V who are eligible for rebleeding-preventive surgery should not be excluded from clazosentan therapy, and physicians should consider administering clazosentan to such patients at their discretion. Also, results of the subpopulation analysis by sex, age group (<65 years, ≥65 years), and body weight (≥30 and <50 kg, ≥50 and <60 kg, ≥60 and <70 kg, ≥70 kg) suggest that these baseline characteristics do not significantly affect the efficacy of clazosentan.

Thus, although no critical factors affecting the efficacy of clazosentan were identified in clinical studies, the package insert will include a statement that no clinical studies have been conducted on the efficacy or safety of clazosentan in patients with WFNS grade V.

PMDA's view:
Since the efficacy of clazosentan was suggested regardless of the size of hematoma, it is acceptable to allow patients with small hematoma to receive clazosentan. However, since the incidence of cerebrovascular spasm-associated M/M events decreases as the hematoma size decreases, whether to administer clazosentan to such patients should be decided by considering the benefit-risk balance.

The efficacy evaluation by aSAH severity suggested that clazosentan had efficacy in both populations of WFNS grade I/II and III/IV, indicating the efficacy of clazosentan regardless of the severity of aSAH. Accordingly, clazosentan should be indicated for the treatment of patients with WFNS grade I to IV. Patients with WFNS grade V (the population excluded from clinical studies) are unlikely to be treated with clazosentan, because Japanese Guidelines for the Management of Stroke 2021 do not aggressively recommend rebleeding-preventive surgery in these patients, and because these patients are at higher risk of pulmonary complications associated with fluid retention. However, given the relationship between the severity of aSAH and the efficacy, clazosentan is expected to have benefits in these patients. Therefore if a patient with WFNS grade V is eligible for rebleeding-preventive surgery, the physician should carefully determine whether to administer clazosentan to the patient after considering the benefit-risk balance of clazosentan and controlling body fluid retention as necessary as described in Section 7.R.3.1.

Thus, within the range investigated in clinical studies, clazosentan is expected to be effective regardless of the size of hematoma and severity of aSAH, the parameters evaluated for the effect on the efficacy. Since the incidence of M/M events varies depending on the size of hematoma and on the

severity of aSAH, and since the clinical studies enrolled only patients with Fisher grade 3 and WFNS grade I to IV, the package insert should include the following statements for appropriate information provision (see Section "7.R.4 Indication and target population"):

(a) Patients eligible for treatment with clazosentan should be carefully selected based on their conditions (e.g., severity of aSAH and size of hematoma), risk of cerebrovascular spasm, and the benefit-risk balance of clazosentan.
(b) The efficacy and safety of clazosentan have not been established in patients with WFNS grade V or patients with any Fisher grade other than grade 3.

7.R.3 Safety

Based on the incidences of adverse events in Japanese and foreign clinical studies and on the following reviews, as well as on the efficacy of clazosentan demonstrated in Section "7.R.2 Efficacy," PMDA concluded that clazosentan has clinically acceptable safety in patients who underwent clipping or coiling for aSAH.

7.R.3.1 Adverse events related to fluid retention

The applicant's explanation about the risk of fluid retention caused by clazosentan:
Clazosentan, an ERA, has a risk of fluid retention, the adverse drug reaction commonly reported with approved ERAs. The incidence of fluid retention-related adverse events[18)] in Studies 306 and 305 was higher in the clazosentan group than in the placebo group, as shown in Table 34. The applicant paid attention to adverse events related to pleural effusion, pulmonary oedema[19)] and cardiac failure[20)] because they are fluid retention-related events significantly affecting hemodynamics.

Table 34 shows the incidences of these events in Studies 306 and 305. The incidence of pleural effusion and pulmonary oedema tended to be higher in the clazosentan group, while the incidence of cardiac failure-related adverse events did not differ between the clazosentan and placebo groups. Among pleural effusion and pulmonary oedema observed, a serious adverse event (pulmonary oedema) was observed in 1 subject in the clazosentan group and considered to be related to the study drug, and its outcome was "recovered." Adverse events leading to discontinuation of the study drug were pulmonary oedema in 5 subjects and pleural effusion in 3 subjects in the clazosentan group. During the perioperative period of aSAH, circulating blood volume and serum protein concentration should be maintained within the normal range, and particular attention should be paid to hyponatraemia (Japanese Guidelines for the Management of Stroke 2021). In recent years, no aggressive treatment to increase fluid volume is performed and, instead, maintaining the fluid at an appropriate level is considered important for controlling the risk of fluid retention.

Based on the above, the risk of clazosentan-induced pleural effusion and pulmonary oedema can be controlled by providing the following precautionary statement in Clinically Significant Adverse Reactions and Important Precautions sections of the draft package insert: "Attention should be paid to the occurrence of pulmonary oedema and pleural effusion, and the balance of fluid volume should be

18) PTs belonging to MedDRA SMQ "haemodynamic oedema, effusions and fluid overload" and PTs of swelling of eyelid, swelling face, eyelid oedema, and face oedema
19) MedDRA PT: pleural effusion, pulmonary oedema
20) PTs belonging to MedDRA SMQ "cardiac failure (narrow)" except PT of pulmonary oedema

maintained during treatment with clazosentan." The incidence of adverse events related to pulmonary complications[21)] was also higher in the clazosentan group than in the placebo group (Table 34), presumably due to the higher incidence of pleural effusion and pulmonary oedema.

In addition to the risk of fluid retention associated with clazosentan, hydrocephalus and brain oedema may occur as complications of aSAH. Table 34 shows the incidences of brain oedema-related adverse events in Studies 306 and 305.[22)] Serious adverse events observed were brain oedema in 4 subjects and hydrocephalus in 3 subjects in the clazosentan group, and brain oedema in 3 subjects, hydrocephalus in 13 subjects, and normal pressure hydrocephalus in 1 subject in the placebo group. Brain oedema in 1 subject in the clazosentan group and brain oedema in 1 subject in the placebo group were considered to be related to the study drug, but the outcome was "recovered" in both of them. Adverse events leading to discontinuation of the study drug was brain oedema occurring in 3 subjects in the clazosentan group. Brain oedema tended to occur at a high incidence in the clazosentan group, and some events of brain oedema were serious or considered to be related to the study drug. Brain oedema was considered to be controllable by taking actions such as appropriate perioperative management, monitoring of brain oedema, and discontinuation of clazosentan administration. However, in patients with brain oedema or intracranial pressure increased, brain oedema may occur or worsen due to the characteristic feature of aSAH. The package insert will include a precaution statement to the effect that patients should be closely monitored and clazosentan should be used carefully.

Table 34 shows the incidences of other adverse events related to fluid retention (other than pleural effusion, pulmonary oedema, and brain oedema)[23)] in Studies 306 and 305. The incidences tended to be higher in the clazosentan group, but there were no serious adverse events or adverse events leading to discontinuation of the study drug. Based on the above, other fluid retention risks will be described in Other Adverse Reactions section of the package insert.

21) PTs belonging to MedDRA HLTs "lower respiratory tract infection bacterial," "conditions associated with abnormal gas exchange," "fungal lower respiratory tract infections," "lower respiratory tract and lung infections," "lower respiratory tract infections NEC," "lower respiratory tract inflammatory and immunologic conditions," "parenchymal lung disorders NEC," "pleural infections and inflammations," "pneumothorax and pleural effusions NEC," "pulmonary hypertensions," "pulmonary oedemas," "pulmonary thrombotic and embolic conditions," "respiratory failures (excl neonatal)," "respiratory tract disorders NEC," "pulmonary vascular disorders NEC," or "viral lower respiratory tract infections," and PTs of bronchospasm, bronchospasm paradoxical, and unilateral bronchospasm.

22) PTs belonging to MedDRA HLGT "increased intracranial pressure and hydrocephalus."

23) PTs belonging to MedDRA SMQ "haemodynamic oedema, effusions and fluid overload" and PTs of swelling of eyelid, swelling face, eyelid oedema, and face oedema. PTs of pleural effusion, pulmonary oedema, and brain oedema were excluded.

Table 34. Incidences of adverse events related to fluid retention or to pulmonary complications

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Adverse events related to fluid retention	14.4 (16)	35.8 (39)	11.7 (13)	33.0 (36)
Pleural effusion	5.4 (6)	15.6 (17)	1.8 (2)	17.4 (19)
Pulmonary oedema	3.6 (4)	10.1 (11)	5.4 (6)	13.8 (15)
Brain oedema	2.7 (3)	8.3 (9)	2.7 (3)	3.7 (4)
Other adverse events related to fluid retention[a, b]	3.6 (4)	14.7 (16)	3.6 (4)	11.0 (12)
Face oedema	0 (0)	1.8 (2)	0 (0)	4.6 (5)
Eyelid oedema	0 (0)	4.6 (5)	0 (0)	0.9 (1)
Oedema	0 (0)	2.8 (3)	0.9 (1)	1.8 (2)
Swelling face	0 (0)	2.8 (3)	0.9 (1)	0 (0)
Swelling of eyelid	1.8 (2)	1.8 (2)	0 (0)	0 (0)
Generalised oedema	0 (0)	0 (0)	0 (0)	1.8 (2)
Adverse events related to cardiac failure	0.9 (1)	1.8 (2)	0.9 (1)	0.9 (1)
Cardiac failure	0 (0)	1.8 (2)	0.9 (1)	0.9 (1)
Cardiac failure congestive	0.9 (1)	0 (0)	0 (0)	0 (0)
Adverse events related to brain oedema	27.0 (30)	18.3 (20)	13.5 (15)	12.8 (14)
Hydrocephalus	21.6 (24)	11.0 (12)	10.8 (12)	9.2 (10)
Brain oedema	2.7 (3)	8.3 (9)	2.7 (3)	3.7 (4)
Cerebrospinal fluid retention	1.8 (2)	0 (0)	0 (0)	0.9 (1)
Normal pressure hydrocephalus	1.8 (2)	0.9 (1)	1.8 (2)	0 (0)
Adverse events related to pulmonary complications[b]	20.7 (23)	33.0 (36)	12.6 (14)	33.0 (36)
Pleural effusion	5.4 (6)	15.6 (17)	1.8 (2)	17.4 (19)
Pulmonary oedema	3.6 (4)	10.1 (11)	5.4 (6)	13.8 (15)
Pneumonia	7.2 (8)	4.6 (5)	3.6 (4)	4.6 (5)
Pneumonia aspiration	4.5 (5)	3.7 (4)	3.6 (4)	0.9 (1)
Pulmonary congestion	0 (0)	3.7 (4)	0.9 (1)	1.8 (2)
Pulmonary embolism	0.9 (1)	0 (0)	0.9 (1)	1.8 (2)
Atelectasis	0.9 (1)	1.8 (2)	0 (0)	1.8 (2)
Hypoxia	0.9 (1)	1.8 (2)	0 (0)	0 (0)

Incidence % (number of subjects with events)
a Fluid retention-related adverse events except MedDRA PTs of pleural effusion, pulmonary oedema, and brain oedema
b Adverse events observed in ≥2 subjects in either of Studies 306 or 305

PMDA asked the applicant to explain the safety of clazosentan administration in combination with systemic circulation improvement therapy (Triple H therapy) or hyperdynamic therapy in clinical studies and to explain the appropriateness of raising caution against fluid retention.

The applicant's explanation:
Only a small number of subjects received clazosentan in combination with Triple H therapy or hyperdynamic therapy either in Study 306 or 305. The incidence of adverse events related to pleural effusion/pulmonary oedema or brain oedema, or adverse events related to cardiac failure was higher in the clazosentan group than in the placebo group, as shown below.

Subjects receiving concomitant Triple H therapy:

Study 306: 41.7% (5 of 12) of subjects in the placebo group and 80.0% (4 of 5) of subjects in the clazosentan group

Study 305: 25.0% (3 of 12) of subjects in the placebo group and 75.0% (3 of 4) of subjects in the clazosentan group

Subjects receiving concomitant hyperdynamic therapy:

Study 306: 20.0% (1 of 5) of subjects in the placebo group and 100% (3 of 3) of subjects in the clazosentan group

Study 305: 50.0% (2 of 4) of subjects in the placebo group and 100% (1 of 1) of subjects in the clazosentan group

In Studies 306 and 305, the fluid balance was targeted at +500 mL or less a day in order to prevent pulmonary complications. But the daily fluid balance exceeded 500 mL in 44.0% to 65.9% of subjects in the clazosentan group who had adverse events related to pleural effusion/ pulmonary oedema or brain oedema, or events related to cardiac failure, showing a tendency of increase. Accordingly, caution will be provided to pay attention to the control of fluid volume during the treatment with clazosentan in the Important Precautions section of the package insert.

PMDA's view:
In Studies 306 and 305, the incidence of pleural effusion and pulmonary oedema tended to be higher in the clazosentan group than in the placebo group. However, it was considered possible to control the risk by adequate perioperative management including the control of body fluid. Accordingly, the applicant's proposal to provide the following precautionary statements in the package insert is generally acceptable:

- Pleural effusion and pulmonary oedema may occur.
- Attention should be paid to fluid volume control.

Given the mechanism of action of clazosentan and occurrences of cardiac failure in clinical studies for which a causal relationship to clazosentan could not be ruled out, healthcare professionals should be appropriately informed that fluid retention-associated cardiac failure may occur as an adverse reaction.

In Studies 306 and 305, the incidence of brain oedema tended to be higher in the clazosentan group than in the placebo group. Patients eligible for treatment with clazosentan are apt to experience brain oedema due to the effect of aSAH, and brain oedema should be listed as a clinically significant adverse reaction in the package insert.

As for other fluid retention-related adverse events (except pleural effusion, pulmonary oedema, and brain oedema), they tended to occur more frequently in the clazosentan group than in the placebo group in Studies 306 and 305. The applicant's proposal to list them as other adverse reactions in the package insert is appropriate.

In Studies 306 and 305, fluid retention-related adverse events such as pleural effusion/pulmonary oedema occurred at a higher rate when clazosentan was administered in combination with Triple H therapy or hyperdynamic therapy, albeit in only a small number of subjects. This should also be mentioned in the package insert, etc., to call attention.

PMDA will draw a final conclusion on this matter, taking account of comments from the Expert Discussion.

7.R.3.2 Adverse events related to haemorrhage

The applicant's explanation about the risk of clazosentan-induced haemorrhage:
Since clazosentan prevents vasoconstriction and is administered to patients after surgery for aSAH for 15 days at the maximum, cases of cerebral haemorrhage were collected in clinical studies as adverse events of special interest. Table 35 shows the incidence of adverse events related to cerebral

haemorrhage[24] and adverse events related to non-cerebral haemorrhage.[25] The incidence of adverse events related to cerebral haemorrhage and the incidence of adverse events related to non-cerebral haemorrhage did not significantly differ between the clazosentan and placebo groups. Among haemorrhage-related adverse events, serious adverse events occurred in the following subjects:

Study 306: Five subjects in the placebo group (subarachnoid haemorrhage in 2 subjects, intraventricular haemorrhage, cerebral haemorrhage, and ruptured cerebral aneurysm in 1 subject each) and in 3 subjects in the clazosentan group (ruptured cerebral aneurysm, subarachnoid haemorrhage, and subdural haematoma in 1 subject each) in the clazosentan group. All events were considered to be unrelated to the study drug.

Study 305: Four subjects in the placebo group (subarachnoid haemorrhage in 3 subjects, vitreous haemorrhage in 1 subject) and in 6 subjects in the clazosentan group (vitreous haemorrhage in 3 subjects, cerebral haemorrhage, retinal haemorrhage, brain stem haemorrhage, and haemorrhage intracranial in 1 subject each). Among them, haemorrhage intracranial in 1 patient in the clazosentan group resulted in treatment discontinuation, and it was considered to be related to the study drug.

In Study AC-054-202, cerebral haemorrhage-related adverse events observed were extradural haematoma or subdural haematoma in 3 subjects in the placebo group (all were nonserious and unrelated to the study drug), extradural haematoma in 1 subject in the clazosentan 5 mg/h group (serious, related to the study drug), and haemorrhagic cerebral infarction in 1 subject in the clazosentan 10 mg/h group (serious, unrelated to the study drug). Haemorrhagic cerebral infarction resulted in discontinuation of the study drug. The incidence of haemorrhage was not higher in the clazosentan group than in the placebo group, either in brain or in sites other than brain, suggesting that clazosentan has no clear risk of causing haemorrhage. Studies 306 and 305 did not enroll “patients with serious intraoperative complication (massive haemorrhage, obstruction of major artery, vascular dissection, vascular injury, large territorial cerebral infarction covering ≥1/3 of vascular territory, etc.)” to avoid clazosentan administration to patients with active haemorrhage. Among patients who had haemorrhage-related adverse events or complications before the start of study drug administration, treatment-emergent adverse events related to haemorrhage occurred in 1 of 8 subjects in the placebo group and in 0 of 11 subjects in the clazosentan group in Study 306; and in 2 of 2 subjects in the placebo group and in 2 of 8 subjects in the clazosentan group in Study 305. Thus, haemorrhage-related adverse events did not tend to occur more frequently in the clazosentan group than in the placebo group.

Caution is raised against haemorrhage as a clinically significant adverse reaction to fasudil hydrochloride hydrate and ozagrel sodium, which are approved for systemic drug therapy against cerebrovascular spasm. There are no clinical study data available on the co-administration of these drugs with clazosentan. Since clazosentan alone has no clear risk of haemorrhage as described above, it is unlikely to enhance the bleeding risk associated with fasudil hydrochloride hydrate or ozagrel sodium when co-administered with these drugs.

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[24] PTs belonging to MedDRA SMQ “haemorrhagic central nervous system vascular conditions”

[25] PTs belonging to MedDRA SMQ “haemorrhage terms (excl laboratory terms)” except PTs of events related to cerebral haemorrhage

Based on the above, the applicant considers that it is unnecessary to raise caution against haemorrhage in the package insert of clazosentan, even for cases where clazosentan is co-administered with fasudil hydrochloride hydrate or ozagrel sodium.

Table 35. Incidences of adverse events related to haemorrhage

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Adverse events related to cerebral haemorrhage	9.0 (10)	2.8 (3)	4.5 (5)	3.7 (4)
Subarachnoid haemorrhage	1.8 (2)	0.9 (1)	2.7 (3)	0 (0)
Cerebral haemorrhage	2.7 (3)	0 (0)	0 (0)	0.9 (1)
Haemorrhage intracranial	0.9 (1)	0 (0)	0.9 (1)	0.9 (1)
Subdural haematoma	0.9 (1)	0.9 (1)	0.9 (1)	0 (0)
Ruptured cerebral aneurysm	0.9 (1)	0.9 (1)	0 (0)	0 (0)
Brain stem haemorrhage	0 (0)	0 (0)	0 (0)	0.9 (1)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0.9 (1)
Extradural haematoma	0.9 (1)	0 (0)	0 (0)	0 (0)
Intraventricular haemorrhage	0.9 (1)	0 (0)	0 (0)	0 (0)
Adverse events related to haemorrhage other than cerebral haemorrhage[a]	8.1 (9)	1.8 (2)	9.0 (10)	9.2 (10)
Vitreous haemorrhage	1.8 (2)	0 (0)	0.9 (1)	4.6 (5)
Retinal haemorrhage	0 (0)	0 (0)	0 (0)	1.8 (2)
Contusion	0 (0)	0 (0)	1.8 (2)	0 (0)
Epistaxis	1.8 (2)	0 (0)	1.8 (2)	0 (0)

Incidence % (number of subjects with events)

a Adverse events observed in ≥2 subjects in either of Study 306 or Study 305

PMDA's view:

Results of Study 306 and Study 305 do not show any tendency of significantly higher risk of haemorrhage-related adverse events in the clazosentan group than in the placebo group. However, clazosentan should be administered only to patients who has received successful hemostatic treatment against aSAH with no further active haemorrhage, for the following reasons:

(a) The target patients for clazosentan therapy are those with vascular injury after invasive treatment for aSAH.

(b) The vasoconstriction-preventive effect of clazosentan may enhance bleeding in patients who have experienced cerebral haemorrhage as an intraoperative complication, a patient group not enrolled in these studies.

(c) Intracranial haemorrhage for which a causal relationship to the study drug could not be ruled out was observed in the clazosentan group in clinical studies.

In the package insert, clazosentan should be contraindicated in patients with intracranial haemorrhage, and caution should be raised against the risk of bleeding. Also, because fasudil hydrochloride hydrate and ozagrel sodium have a known bleeding risk, clazosentan, when co-administered with either of these drugs, may aggravate the bleeding even if clazosentan alone does not induce bleeding. Appropriate caution should be raised regarding the co-administration of clazosentan with these drugs.

PMDA will draw a final conclusion on this matter, taking account of comments from the Expert Discussion.

7.R.3.3 Adverse events related to hypotension

The applicant's explanation about the risk of clazosentan-induced hypotension:

Clazosentan may decrease blood pressure through its effect to prevent vasoconstriction. Table 36 shows the incidences of hypotension-related adverse events[26)] in Studies 306 and 305. In Study 305, death due to decreased blood pressure occurred in 1 subject in the clazosentan group. No other serious hypotension-related adverse events were observed. The subject who died presented with decreased blood pressure accompanied by pupillary dilatation on Day 7 after the start of clazosentan administration, and then discontinued to receive clazosentan; marked brain oedema was detected by CT on Day 8 and the subject died on Day 10. The decreased blood pressure was considered to be related to the intracranial lesion and unrelated to clazosentan. Taking account of the above results and the exclusion of patients with treatment-resistant hypotension (systolic pressure <90 mmHg at screening) from clinical studies, the Important Precautions section of the package insert will include the following precautionary statement: "Blood pressure should be monitored before and during clazosentan administration and, if blood pressure cannot be controlled appropriately, the administration should be avoided or discontinued."

Table 36. Incidences of hypotension-related adverse events

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Hypotension-related adverse events	0 (0)	2.8 (3)	0 (0)	5.5 (6)
Hypotension	0 (0)	2.8 (3)	0 (0)	4.6 (5)
Blood pressure decreased	0 (0)	0 (0)	0 (0)	0.9 (1)
Hypovolaemic shock	0 (0)	0.9 (1)	0 (0)	0 (0)

Incidence % (number of events with events)

PMDA's view:

The applicant's proposal to include the following precautionary statements in the package insert is appropriate:

(a) Clazosentan should not be administered if blood pressure cannot be controlled appropriately before the start of clazosentan administration.

(b) Blood pressure should be monitored during clazosentan administration, and the administration should be discontinued if blood pressure cannot be controlled.

7.R.3.4 Anaemia-related adverse events

The applicant's explanation about the risk of clazosentan-associated anaemia:

Cautions are raised against anaemia/decreased hemoglobin as clinically significant adverse reactions to approved ERAs (these reactions are considered to be caused by increased plasma volume). Table 37 shows the incidences of anaemia-related adverse events[27)] in Studies 306 and 305. The incidence of anaemia tended to be higher in the clazosentan group than in the placebo group. There were no serious adverse events or adverse events leading to discontinuation of the study drug. All adverse events were mild or moderate except severe anaemia observed in 1 subject in the clazosentan group. The change

26) PTs containing the term "blood pressure" and "decreased," PTs containing the term "hypotension" (except intracranial hypotension and neonatal hypotension), PTs of blood pressure immeasurable, mean arterial pressure decreased, circulatory collapse, and the following PTs containing the term "shock": Cardiogenic shock, distributive shock, hypovolaemic shock, procedural shock, shock, shock haemorrhagic, and shock symptom.

27) PTs belonging to MedDRA SMQ "haematopoietic erythropenia" or in SMQ "haematopoietic cytopenias affecting more than 1 type of blood cell," PTs containing the term "anaemia," and PT of haemodilution.

(mean ± SD) in hemoglobin level from baseline to the end of the study drug administration was −2.0 ± 13.9 g/L in the placebo group and −9.7 ± 12.6 g/L in the clazosentan group in Study 306; and −2.2 ± 12.9 g/L in the placebo group and −10.0 ± 13.0 g/L in the clazosentan group in Study 305, showing a greater decrease in the clazosentan group. Patients after surgery for aSAH are hospitalized during clazosentan administration, and therefore their hemoglobin levels can be controlled. Accordingly, the Important Precautions section of the package insert will include the following precautionary statement: "Hemoglobin levels should be measured before clazosentan administration and, as necessary, during clazosentan administration, and appropriate actions should be taken if any abnormality is noticed."

Table 37. Incidence of anaemia-related adverse events

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Anaemia-related adverse events	14.4 (16)	18.3 (20)	6.3 (7)	14.7 (16)
Anaemia	13.5 (15)	18.3 (20)	5.4 (6)	14.7 (16)
Anaemia postoperative	0.9 (1)	0 (0)	0 (0)	0 (0)
Pancytopenia	0 (0)	0 (0)	0.9 (1)	0 (0)

Incidence % (number of subjects with events)

PMDA's view:

In Studies 306 and 305, the incidence of anaemia-related adverse events was higher in the clazosentan group than in the placebo group. Clazosentan has a risk of causing fluid retention, a risk affecting hemodynamics. Given that anaemia is an important factor adversely affecting worsened hemodynamics associated with fluid retention, due attention should be paid to the occurrence of anaemia. Therefore, the applicant's proposal to include the following precautionary statement in the package insert is generally appropriate: "Hemoglobin level should be measured before clazosentan administration and, as necessary, during clazosentan administration, and appropriate actions such as treatment discontinuation should be taken if any abnormality is observed."

7.R.3.5 Adverse events related to liver disorder

The applicant's explanation about the risk of liver disorder caused by clazosentan:

Cases of serious hepatic dysfunction have been reported in patients receiving approved ERAs. Therefore data on hepatic dysfunction were collected as adverse events of special interest in the clinical studies of clazosentan. Table 38 shows the incidences of liver disorder-related adverse events[28)] in Studies 306 and 305. In Study 306, the incidence of liver disorder-related adverse events was lower in the clazosentan group than in the placebo group. All adverse events were nonserious, and were mild or moderate except for 1 event (severe liver function test abnormal related to the study drug) in 1 subject in the clazosentan group. In Study 305, the incidence of liver disorder-related adverse events was higher in the clazosentan group than in the placebo group, but all events were nonserious and their severity was mild or moderate except for 1 event (severe ascites related to the study drug) in 1 subject in the clazosentan group. The study drug administration could be continued in most of the subjects. An adverse event leading to discontinuation of the study drug occurred in 1 subject in the clazosentan group (ascites). The approved ERAs, which are indicated for pulmonary arterial hypertension (PAH), are administered for a long period, whereas clazosentan is indicated for

[28)] PTs belonging to MedDRA SMQ "hepatic disorders"

patients after surgery for aSAH and administered until Day 15 after aSAH onset. Accordingly, it is unnecessary to require periodical hepatic function test. Precautions for hepatic function abnormal will be included in Other Adverse Reactions section of the package insert.

Table 38. Incidence of adverse events related to liver disorder

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Adverse events related to liver disorder	52.3 (58)	42.2 (46)	22.5 (25)	35.8 (39)
Hypoalbuminaemia	19.8 (22)	18.3 (20)	5.4 (6)	16.5 (18)
Hepatic function abnormal	9.0 (10)	9.2 (10)	3.6 (4)	6.4 (7)
Hepatic enzyme increased	3.6 (4)	1.8 (2)	9.0 (10)	9.2 (10)
Liver function test abnormal	8.1 (9)	10.1 (11)	0.9 (1)	0 (0)
Liver function test increased	14.4 (16)	7.3 (8)	1.8 (2)	2.8 (3)
ALT increased	2.7 (3)	1.8 (2)	3.6 (4)	1.8 (2)
Ascites	0 (0)	0 (0)	0.9 (1)	3.7 (4)
AST increased	0.9 (1)	0.9 (1)	2.7 (3)	1.8 (2)
Drug-induced liver injury	0.9 (1)	0.9 (1)	0 (0)	0.9 (1)
γ-GTP increased	0.9 (1)	0 (0)	0 (0)	0.9 (1)
Liver disorder	2.7 (3)	0 (0)	0 (0)	0 (0)

Incidence % (number of subjects with events)

PMDA's view:

The incidence of hepatic dysfunction-related adverse events was higher in the clazosentan group than in the placebo group in Study 305, and a severe hepatic dysfunction-related adverse events occurred in Study 306 as well. These findings suggest that clazosentan may have a risk of causing liver disorder, as with approved ERAs. On the other hand, clazosentan is administered for only a short period (until Day 15 after aSAH onset) to inpatients whose conditions, including hepatic function tests, are managed in hospital. Therefore, at present, there is little need to require periodical hepatic function tests. Hepatic dysfunction-related adverse events should be listed as other adverse reactions and their incidences should be provided in the package insert.

7.R.3.6 Adverse events related to tachyarrhythmia

The applicant's explanation about the risk of tachyarrhythmia caused by clazosentan:

In the foreign QT study conducted in healthy adults, QT interval prolongation was observed [see Section "6.R.2 QT interval-prolonging effect of clazosentan"]. Accordingly, cases of tachyarrhythmia-related adverse events were collected as adverse events of special interest in the clinical studies of clazosentan. Table 39 shows the incidences of tachyarrhythmia-related adverse events[29)] in Studies 306 and 305.

[29)] PTs belonging to MedDRA SMQ "tachyarrhythmia (incl. supraventricular and ventricular tachyarrhythmias) or SMQ "Torsade de pointes/QT prolongation (broad)"

Table 39. Incidence of adverse events related to tachyarrhythmia

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
Adverse events related to tachyarrhythmia	6.3 (7)	0.9 (1)	2.7 (3)	2.8 (3)
Atrial fibrillation	2.7 (3)	0 (0)	1.8 (2)	1.8 (2)
Supraventricular tachycardia	1.8 (2)	0 (0)	0 (0)	0.9 (1)
Ventricular extrasystoles	0 (0)	0.9 (1)	0 (0)	0 (0)
Torsade de pointes	0 (0)	0 (0)	0.9 (1)	0 (0)
Ventricular fibrillation	0.9 (1)	0 (0)	0 (0)	0 (0)
Electrocardiogram QT prolonged	0.9 (1)	0 (0)	0.9 (1)	0 (0)

Incidence % (number of subjects with events)

Table 40 shows QTc assessment in Studies 306 and 305. QTc interval tended to be longer in the clazosentan group than in the placebo group in Study 305. On the other hand, tachyarrhythmia-associated adverse events related to QTc interval prolongation were not observed. Currently, it is considered appropriate to include, in the Important Precautions section of the package insert, precautionary statements regarding QT interval prolongation and the advice to perform electrocardiography before and during clazosentan administration.

Table 40. QTc assessment

	Study 306		Study 305	
	Placebo (n = 111)	Clazosentan (n = 109)	Placebo (n = 111)	Clazosentan (n = 109)
No. of subjects analyzed for QTcF	109	107	109	109
ΔQTcF (mean ± SD)[a]	−4.6 ± 39.3	−12.2 ± 36.8	−16.2 ± 46.6	−19.4 ± 44.1
QTcF >450 ms[b]	16.5 (18)	15.9 (17)	16.5 (18)	23.9 (26)
QTcF >480 ms[b]	2.8 (3)	2.8 (3)	6.4 (7)	5.5 (6)
QTcF >500 ms[b]	0.9 (1)	1.9 (2)	3.7 (4)	3.7 (4)
ΔQTcF >30 ms[a, b]	24.8 (27)	27.1 (29)	20.2 (22)	24.8 (27)
ΔQTcF >60 ms[a, b]	3.7 (4)	7.5 (8)	7.3 (8)	6.4 (7)
No. of subjects analyzed for QTcB	109	107	109	109
ΔQTcB (mean ± SD)[a]	−1.7 ± 40.6	−4.8 ± 39.5	−14.7 ± 42.6	−8.9 ± 45.6
QTcB >450 ms[b]	32.1 (35)	27.1 (29)	24.8 (27)	40.4 (44)
QTcB >480 ms[b]	6.4 (7)	10.3 (11)	8.3 (9)	14.7 (16)
QTcB >500 ms[b]	1.8 (2)	1.9 (2)	5.5 (6)	4.6 (5)
ΔQTcB >30 ms[a, b]	30.3 (33)	32.7 (35)	17.4 (19)	35.8 (39)
ΔQTcB >60 ms[a, b]	8.3 (9)	9.3 (10)	5.5 (6)	11.9 (13)

Incidence % (number of subjects with events)

a Change from baseline to the end of study drug administration

b Percentage of subjects who showed abnormality during treatment after the start of study drug administration

PMDA's view:

In Studies 306 and 305, the incidence of tachyarrhythmia-related adverse events did not significantly differ between the clazosentan group and the placebo group, but QT assessment by electrocardiogram showed a tendency of QTc interval prolongation in the clazosentan group compared with the placebo group. Accordingly, PMDA considers that the applicant's proposal to recommend electrocardiography before and during clazosentan administration in the package insert, is appropriate.

7.R.3.7 Safety in elderly patients

The applicant's explanation about the safety in elderly patients:

Table 41 shows the incidences of adverse events by age group in Studies 306 and 305. The incidence of pleural effusion did not differ between age subgroups. In both clinical studies, patients aged ≥65 years receiving clazosentan had a higher incidence of pulmonary oedema than patients aged ≥65 years

receiving placebo and patients aged <65 years receiving clazosentan. In response to these results, the package insert will include a precautionary statement that the risk of pulmonary oedema increases in elderly patients aged ≥65 years. No particular precautions are required for other adverse events of special interest in elderly patients because there were no events with a significantly higher incidence in patients aged ≥65 years receiving clazosentan than in those aged <65 years receiving clazosentan.

Table 41. Incidences of adverse events by age group

	Study 306				Study 305			
	<65		≥65		<65		≥65	
	Placebo (n = 67)	Clazosentan (n = 75)	Placebo (n = 44)	Clazosentan (n = 34)	Placebo (n = 77)	Clazosentan (n = 78)	Placebo (n = 34)	Clazosentan (n = 31)
Adverse events	98.5 (66)	98.7 (74)	93.2 (41)	100.0 (34)	93.5 (72)	92.3 (72)	91.2 (31)	83.9 (26)
Adverse events leading to death within 12 weeks after aSAH onset	3.0 (2)	0 (0)	0 (0)	2.9 (1)	1.3 (1)	2.6 (2)	5.9 (2)	0 (0)
Serious adverse events	26.9 (18)	13.3 (10)	15.9 (7)	32.4 (11)	18.2 (14)	16.7 (13)	20.6 (7)	12.9 (4)
Adverse events leading to discontinuation of the study drug	11.9 (8)	12.0 (9)	13.6 (6)	17.6 (6)	11.7 (9)	9.0 (7)	8.8 (3)	9.7 (3)
Pleural effusion	6.0 (4)	17.3 (13)	4.5 (2)	11.8 (4)	0 (0)	15.4 (12)	5.9 (2)	22.6 (7)
Pulmonary oedema	3.0 (2)	5.3 (4)	4.5 (2)	20.6 (7)	3.9 (3)	10.3 (8)	8.8 (3)	22.6 (7)
Brain oedema	4.5 (3)	8.0 (6)	0 (0)	8.8 (3)	2.6 (2)	1.3 (1)	2.9 (1)	9.7 (3)
Other adverse events related to fluid retention[a]	3.0 (2)	13.3 (10)	4.5 (2)	17.6 (6)	3.9 (3)	10.3 (8)	2.9 (1)	12.9 (4)
Adverse events related to hypotension	0 (0)	2.7 (2)	0 (0)	2.9 (1)	0 (0)	5.1 (4)	0 (0)	6.5 (2)
Adverse events related to anaemia	10.4 (7)	17.3 (13)	20.5 (9)	20.6 (7)	6.5 (5)	10.3 (8)	5.9 (2)	25.8 (8)
Adverse events related to cerebral haemorrhage	10.4 (7)	0 (0)	6.8 (3)	8.8 (3)	3.9 (3)	2.6 (2)	5.9 (2)	6.5 (2)
Adverse events related to haemorrhage other than cerebral haemorrhage	6.0 (4)	0 (0)	11.4 (5)	5.9 (2)	7.8 (6)	10.3 (8)	11.8 (4)	6.5 (2)
Adverse events related to liver disorder	56.7 (38)	48.0 (36)	45.5 (20)	29.4 (10)	24.7 (19)	33.3 (26)	17.6 (6)	41.9 (13)
Adverse events related to tachyarrhythmia	6.0 (4)	0 (0)	6.8 (3)	2.9 (1)	1.3 (1)	1.3 (1)	5.9 (2)	6.5 (2)

Incidence % (number of subjects with events)
a Fluid retention-related adverse events except MedDRA PTs of pleural effusion, pulmonary oedema and brain oedema

PMDA's view:

The following applicant's proposal based on the incidence of adverse events by age group in Studies 306 and 305 are acceptable: The package insert will include a precautionary statement regarding fluid retention-related adverse events such as pulmonary oedema in elderly patients aged ≥65 years.

7.R.4 Indication and target population

The applicant provided the following rationale for the proposed indication of clazosentan: "Prevention of cerebrovascular spasm after treatment of subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes":

(a) Indication

Causative diseases of SAH include, in addition to cerebral aneurysm, traumatic SAH, cerebral arteriovenous malformation, etc., and the clinical course after the onset of SAH do not seem to differ significantly between patients with different causative diseases. However, the clinical studies of clazosentan enrolled only patients with aSAH, for the following reasons:

(a) In total, 85% of idiopathic SAH cases are caused by cerebral aneurysm.
(b) When the clinical studies were planned, no sufficient information was available on the incidence or prognosis of cerebrovascular spasm after SAH caused by factors other than cerebral aneurysm.

In Studies 306 and 305 in patients who underwent clipping or coiling for aSAH, the incidence of cerebrovascular spasm-related M/M events, a primary endpoint, was significantly lower in the clazosentan group than in the placebo group, and the incidences of the components of M/M events (i.e., cerebrovascular spasm-associated new cerebral infarction and cerebrovascular spasm-associated DIND) were also lower in the clazosentan group than in the placebo group. The incidence of moderate or severe cerebrovascular spasm, the secondary endpoint, was also lower in the clazosentan group than in the placebo group. Given the patient population of the clinical studies of clazosentan and the demonstrated efficacy, the indication of clazosentan should be as follows: "Prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes."

(b) Patient populations excluded from the clinical studies

The applicant's explanation about clazosentan administration to patient populations excluded from the clinical studies:

Since patients with large territorial cerebral infarction (including perioperative cerebral infarction) are likely to affect efficacy assessment, patients with large territorial cerebral infarction due to surgery were excluded from the clinical studies. In clinical practice, however, it is unnecessary to exclude this patient group from treatment with clazosentan because, in some cases, the benefit of preventing cerebrovascular spasm by clazosentan may be considered to outweigh the risk of the drug by the treating physician.

Patients with a stent in the intracranial major artery were excluded from the clinical studies to avoid a possible effect on efficacy assessment. In clinical practice, post-operative prevention of cerebrovascular spasm is necessary also in patients who received a stent for coiling. Since 2 types of antiplatelet agents are administered before stenting, the safety of co-administration of clazosentan and these drugs was investigated. An antiplatelet agent(s) (aspirin, clopidogrel, or cilostazol) was co-administered with clazosentan to 14.4% (16 of 111) of subjects in the placebo group and to 3.7% (4 of 109) of subjects in the clazosentan group in Study 306; and to 49.5% (55 of 111) of subjects in the placebo group and to 45.0% (49 of 109) of subjects in the clazosentan group in Study 305. Table 42 shows the incidences of adverse events in subjects with or without co-administration of antiplatelet agents. Subjects receiving clazosentan plus an antiplatelet agent(s) did not show a tendency of higher incidence of adverse events than those receiving placebo plus an antiplatelet agent(s). Two antiplatelet agents were co-administered with clazosentan to 1 subject in the placebo group of Study 306 and to 21.8% (12 of 55) of subjects in the placebo group and to 16.3% (8 of 49) of subjects in the clazosentan

group in Study 305. Among subjects receiving co-administration of 2 antiplatelet agents and clazosentan or placebo in Study 305, the incidence of adverse events was 91.7% (11 of 12) of subjects in the placebo group and 87.5% (7 of 8) of subjects in the clazosentan group, the incidence of cerebral haemorrhage-related adverse events was 8.3% (1 of 12) of subjects in the placebo group and 0% (0 of 8) of subjects in the clazosentan group, and the incidence of adverse events related to haemorrhage other than cerebral haemorrhage was 25.0% (3 of 12) of subjects in the placebo group and 12.5% (1 of 8) of subjects in the clazosentan group. These results show no trend towards higher incidence of adverse events in the clazosentan group than in the placebo group. Since no data suggest that clazosentan may increase the risk of haemorrhage in patients with vascular injuries after surgery for aSAH [see Section "7.R.3.2 Adverse events related to haemorrhage"], it is unnecessary to exclude patients who have received a stent from the eligible population for clazosentan. Also, no particular precaution is necessary regarding co-administration of antiplatelet agents with clazosentan.

Table 42. Incidence of adverse events in subjects with or without co-administration of antiplatelet agent

	Co-administration of antiplatelet agent	Study 306		Study 305	
		Placebo	Clazosentan	Placebo	Clazosentan
Adverse events	Yes	100 (16/16)	100 (4/4)	90.9 (50/55)	85.7 (42/49)
	No	95.8 (91/95)	99.0 (104/105)	94.6 (53/56)	93.3 (56/60)
Cerebral haemorrhage-related adverse events	Yes	12.5 (2/16)	0 (0/4)	3.6 (2/55)	0 (0/49)
	No	8.4 (8/95)	2.9 (3/105)	5.4 (3/56)	6.7 (4/60)
Adverse events related to haemorrhage other than cerebral haemorrhage	Yes	0 (0/16)	0 (0/4)	12.7 (7/55)	6.1 (3/49)
	No	9.5 (9/95)	1.9 (2/105)	5.4 (3/56)	11.7 (7/60)

PMDA's view:

Given the subjects included in the clinical studies of clazosentan and the efficacy results obtained, it is reasonable to limit the eligible population for clazosentan to those with aSAH (i.e., not all patients with SAH) with the following indication: "Prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes." The clinical studies of clazosentan were conducted in patients who received either clipping or coiling, both of which are operative methods used to prevent re-bleeding from cerebral aneurysm and have been shown to be effective and safe [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. It is therefore unnecessary to limit the indication to either of the operative methods. However, it should be made mandatory to confirm that haemostasis has been achieved appropriately by a surgical treatment for aSAH. The applicant's explanation about the appropriateness of clazosentan administration to the population excluded from the clinical studies is acceptable. However, patients with large territorial cerebral infarction (including perioperative cerebral infarction) should be treated with clazosentan only if the benefit of clazosentan, including the improvement of functional prognosis, outweighs the risk.

Based on the above review and on the review in Section 7.R.2.3, the Indication and Precautions Concerning Indication should be as follows:

Indication

Prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes

Precautions Concerning Indication

- Clazosentan should be administered to patients who have achieved hemostasis appropriately by surgical or endovascular treatment against ruptured cerebral aneurysm.
- Whether to administer clazosentan should be decided based on the severity of subarachnoid haemorrhage, size of hematoma, the range of cerebral infarction (including perioperative cerebral infarction), and other conditions of the patient. The efficacy and safety of clazosentan have not been established in the following patients:
  - Patients with World Federation of Neurosurgical Surgeons grade V
  - Patients with large territorial cerebral infarction
  - Patients other than those with Fisher grade 3

7.R.5 Dosage and administration

The applicant's rationale for the proposed dosage and administration:

Cerebrovascular spasm most frequently occur within 15 days of aSAH onset (*Neurosurg.* 2006;29:179-93, *CNS Neurosci Ther.* 2019;25:1096-112). Accordingly, clazosentan should be administered as soon as possible after aSAH onset in patients who have appropriately completed the surgery to prevent rebleeding after aSAH, with the treatment period from the onset of aSAH to Day 15.

In foreign countries, a dose-finding study (Study AC-054-201[7)]) was conducted in patients who underwent clipping or coiling for aSAH, and the results of the incidence of moderate or severe cerebrovascular spasm within 14 days after aSAH onset, the primary endpoint, were evaluated separately in patients undergoing clipping and those undergoing coiling. Based on this evaluation, clazosentan 5 mg/h was used in the foreign phase III study in patients who underwent clipping for aSAH (Study AC-054-301[5)]), and clazosentan 5 mg/h and 15 mg/h were used in the foreign phase III study in patients who underwent coiling for aSAH (Study AC-054-302[6)]).

In Japan, a dose-finding study was conducted in Japanese and South Korean patients who underwent clipping for aSAH (Study AC-054-202). In the foreign Study AC-054-201, the 15 mg/h dose showed the maximal efficacy was in the entire population, but pulmonary complications occurred frequently in all clazosentan dose groups (27.1% [26 of 96] of subjects in the placebo group, 43.9% [47 of 107] of subjects in the clazosentan 1 mg/h group, 43.6% [48 of 110] of subjects in the clazosentan 5 mg/h group, 38.5% [37 of 96] of subjects in the clazosentan 15 mg/h group). Accordingly, Study AC-054-202 investigated only the 5 mg/h and 10 mg/h doses for safety purposes. The results showed that the incidence of moderate or severe cerebrovascular spasm within 14 days after aSAH onset was lower in both clazosentan 5 mg/h and 10 mg/h groups than in the placebo group, and the incidence of cerebrovascular spasm-related M/M events was also lower in the clazosentan 10 mg/h group than in the placebo group. No clinically significant difference was observed in the incidence of adverse events between the clazosentan 5 mg/h group and 10 mg/h group. The incidence of moderate or severe cerebrovascular spasm tended to decrease dose-dependently in the entire population and in the Japanese population, whereas in the South Korean population, the maximal effect was observed in the 5 mg/h group. However, this difference is unlikely to suggest the difference in dose-response between

Japanese and non-Japanese patients, given that (a) the evaluation of dose-response relationship was limited because of the small number of subjects in each subpopulation, and (b) the incidence of cerebrovascular spasm-related M/M events tended to decrease dose-dependently in both subpopulations. Also, there is no significant difference between Japanese and South Korean subjects in the intrinsic and extrinsic ethnic factors such as PK of clazosentan [see Section "6.R.1 Similarity of PK between Japanese and South Korean subjects"], patient characteristics (sex, body weight, WFNS grade, size of hematoma, time from the onset of aSAH to the start of clazosentan administration, duration of surgery, etc.), diagnostic criteria and severity classification, and medical environment of stroke treatment, except that nimodipine is yet to be approved in Japan. In addition, the incidence of moderate or severe cerebrovascular spasm in the placebo group was similar in Japanese and South Korean subjects. It is therefore appropriate that Study AC-054-202 was conducted as a joint Japanese and South Korean study and that the efficacy and safety in Japanese subjects is investigated based on the results of the entire population. Based on the above, the 10 mg/h dose was selected in Study 306 (the Japanese phase III study) in Japanese patients after clipping. Although there were no data on the incidence of M/M events in Japanese patients after coiling for aSAH or on the recommended dose in this patient group, Study 305 used the same dose as in Study 306 based on the following assumptions: The incidence of M/M events and the mechanism of the onset of cerebrovascular spasm are similar in patients after clipping and those after coiling, judging from the results of the foreign phase III studies (Studies AC-054-301 and AC-054-302), and the efficacy of clazosentan is similar in patients after coiling and patients after clipping.

Results of Studies 306 and 305 demonstrated the efficacy of clazosentan 10 mg/h with acceptable safety profile. Accordingly, it is appropriate to administer clazosentan at the speed of 10 mg/h to patients after either coiling or clipping until Day 15 after aSAH onset.

The applicant's explanation about the timing of initiating clazosentan after surgery for aSAH:
Study AC-054-202 and other foreign clinical studies included patients who could receive clazosentan within 56 hours after aSAH onset, in order to allow time for transportation of patients to medical institutions, diagnosis and tests, the duration of surgery for subarachnoid haemorrhage. In clinical settings in Japan, the acceptance of patients with cerebral stroke and acute phase treatment are common procedures; therefore in Studies 306 and 305, the study drug administration was initiated within 48 hours after aSAH onset to evaluate the efficacy of treatment in subjects with characteristics as uniform as possible. The mean time from the onset of aSAH to the start of surgery for aSAH was 13.2 hours in the placebo group and 13.7 hours in the clazosentan group in Study 306; and 12.3 hours in the placebo group and 11.7 hours in the clazosentan group in Study 305. The mean duration of surgery for aSAH was 5.4 hours in both the placebo and clazosentan groups in Study 306; and 2.5 hours in the placebo group and 2.4 hours in the clazosentan group in Study 305. Tables 43 and 44 show the incidence of cerebrovascular spasm-related M/M events and of adverse events, classified by the time from aSAH onset to the start of study drug administration in Studies 306 and 305 and Study AC-054-202. In Studies 306 and 305, the number of subjects receiving the study drug <24 hours after aSAH onset was limited; this made it difficult to compare the incidence of M/M events between the populations receiving the study drug ≥24 hours and <24 hours after aSAH onset. However, there were no efficacy or safety concerns related to the time lapse after the onset. As for the efficacy and safety of

clazosentan administered >48 after aSAH onset, results of the subpopulation analysis in Study AC-054-202 showed a tendency of a decrease in cerebrovascular spasm-related M/M events even in subjects receiving clazosentan 48 to 56 hours after aSAH onset without any significant difference in safety. These results suggest the clinical significance of administering clazosentan 48 to 56 hours after aSAH onset in clinical practice. Thus, it is unnecessary to limit the timing of clazosentan administration to "within 48 hours after aSAH onset." Nevertheless, for achieving the purpose of clazosentan therapy, the administration should be started as soon as possible after aSAH onset in patients who have appropriately completed surgery for preventing rebleeding after aSAH. The package insert will state that administration of clazosentan should be started roughly within 48 hours after aSAH onset.

Table 43. Efficacy and safety by time between aSAH onset and the start of administration in Studies 306 and 305

	Time between aSAH onset and the start of administration	Study 306		Study 305	
		Placebo	Clazosentan 10 mg/h	Placebo	Clazosentan 10 mg/h
Cerebrovascular spasm-related M/M events	<24 h	16.7 (1/6)	50.0 (1/2)	25.0 (4/16)	10.0 (1/10)
	≥24 to <48 h	41.0 (41/100)	15.5 (16/103)	29.5 (28/95)	14.0 (13/93)
Adverse events	<24 h	100.0 (5/5)	100.0 (2/2)	93.8 (15/16)	72.7 (8/11)
	≥24 and <48 h	96.2 (102/106)	99.1 (106/107)	92.6 (88/95)	91.8 (90/98)
Pleural effusion/pulmonary oedema	<24 h	40.0 (2/5)	50.0 (1/2)	12.5 (2/16)	18.2 (2/11)
	≥24 and <48 h	7.5 (8/106)	22.4 (24/107)	5.3 (5/95)	27.6 (27/98)
Brain oedema	<24 h	0 (0/5)	50.0 (1/2)	0 (0/16)	0 (0/11)
	≥24 and <48 h	2.8 (3/106)	7.5 (8/107)	3.2 (3/95)	4.1 (4/98)
Other fluid retention-related adverse events	<24 h	0 (0/5)	0 (0/2)	0 (0/16)	0 (0/11)
	≥24 and <48 h	3.8 (4/106)	15.0 (16/107)	4.2 (4/95)	12.2 (12/98)
Cerebral haemorrhage-related adverse events	<24 h	0 (0/5)	0 (0/2)	6.3 (1/16)	0 (0/11)
	≥24 and <48 h	9.4 (10/106)	2.8 (3/107)	4.2 (4/95)	4.1 (4/98)
Adverse events related to haemorrhage other than cerebral haemorrhage	<24 h	20.0 (1/5)	0 (0/2)	6.3 (1/16)	0 (0/11)
	≥24 and <48 h	7.5 (8/106)	1.9 (2/107)	9.5 (9/95)	10.2 (10/98)

Table 44. Efficacy and safety by time between aSAH onset and the start of administration in Study AC-054-202

	Time between aSAH onset and the start of administration	Study AC-054-202		
		Placebo	Clazosentan 5 mg/h	Clazosentan 10 mg/h
Cerebrovascular spasm-related M/M events	≤48 h	39.5 (15/38)	21.1 (8/38)	8.6 (3/35)
	>48 h	43.8 (7/16)	21.4 (3/14)	21.4 (3/14)
Adverse events	≤48 h	95.2 (40/42)	95.0 (38/40)	95.2 (40/42)
	>48 h	88.9 (16/18)	100.0 (20/20)	94.1 (16/17)
Pleural effusion/pulmonary oedema	≤48 h	11.9 (5/42)	27.5 (11/40)	19.0 (8/42)
	>48 h	5.6 (1/18)	15.0 (3/20)	11.8 (2/17)
Brain oedema	≤48 h	0 (0/42)	12.5 (5/40)	7.1 (3/42)
	>48 h	0 (0/18)	5.0 (1/20)	5.9 (1/17)
Other fluid retention-related adverse events	≤48 h	4.8 (2/42)	7.5 (3/40)	11.9 (5/42)
	>48 h	5.6 (1/18)	20.0 (4/20)	5.9 (1/17)
Cerebral haemorrhage-related adverse events	≤48 h	4.8 (2/42)	0 (0/40)	0 (0/42)
	>48 h	5.6 (1/18)	5.0 (1/20)	5.9 (1/17)
Adverse events related to haemorrhage other than cerebral haemorrhage	≤48 h	9.5 (4/42)	7.5 (3/40)	11.9 (5/42)
	>48 h	11.1 (2/18)	5.0 (1/20)	5.9 (1/17)

PMDA's view:

The dosage of clazosentan should be "administration at the speed of 10 mg/h until Day 15 after aSAH onset"; this dosage was shown to be effective and safe in Studies 306 and 305. Since clazosentan may

enhance haemorrhage through its effect of preventing vasoconstriction, it is reasonable to start the administration as soon as possible after hemostasis is achieved by surgery performed to prevent rebleeding after aSAH. In Studies 306 and 305, clazosentan was to be administered within 48 hours after aSAH onset. In the studies, clazosentan administered early after surgery did not pose any safety concerns and, albeit in a limited number of subjects, the studies suggested the efficacy of clazosentan administered ≥48 hours after aSAH onset as well. Based on these findings, physicians should be advised to start administration as soon as possible, preferably but not exclusively within 48 hours of aSAH onset, after examining the patient's postoperative conditions.

On the basis of the reviews above and in Sections 6.R.3 and 6.R.4, the Dosage and Administration and the Precautions Concerning Dosage and Administration should be as follows:

Dosage and Administration

The usual adult dosage is 300 mg (12 mL) of clazosentan diluted with 500 mL of physiological saline, continuously administered intravenously at the speed of 17 mL/h (clazosentan 10 mg/h) using a constant infusion pump. Administration of clazosentan is started early after surgery for subarachnoid haemorrhage and continued until Day 15 after the onset of subarachnoid haemorrhage. The dose may be reduced depending on the liver function and concomitant medications.

Precautions Concerning Dosage and Administration

- Administration of clazosentan should be started within 48 hours after the onset of subarachnoid haemorrhage, as a rough guide.
- Whether to administer clazosentan to patients with moderate hepatic impairment (Child-Pugh class B) should be assessed carefully and, if it is administered, the dose should be reduced to half the usual dose (clazosentan 5 mg/h). The dosage for such patients is 150 mg of clazosentan diluted with 500 mL of physiological saline, administered intravenously at the speed of 17 mL/h using a constant infusion pump until Day 15 after the onset of subarachnoid haemorrhage.
- Co-administration of clazosentan and rifampicin should be avoided unless therapeutically mandated. If concomitant rifampicin is administered, the dose of clazosentan should be reduced to a quarter of the usual dose (2.5 mg/h), patients should be carefully monitored, and due attention should be paid to the occurrence of adverse drug reactions. The dosage for patients receiving concomitant rifampicin is 150 mg of clazosentan diluted with 500 mL of physiological saline, administered intravenously at the speed of 8.5 mL/h using a constant infusion pump until Day 15 after the onset of subarachnoid haemorrhage.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing investigations on clazosentan:

Taking account of the mechanism of action of clazosentan, results of nonclinical studies, and the incidence of adverse events in clinical studies, the risk management plan (draft) will include the following safety specifications: Pulmonary complication/fluid retention, hypotension/blood pressure decreased, anaemia/haemoglobin decreased, hepatic function abnormal, teratogenicity, tachyarrhythmia (ventricular and supraventricular arrhythmias including QT prolongation). After the marketing of clazosentan, a use-result survey will be conducted to investigate the incidences of these

adverse events in clinical use, with the planned sample size of 2000 (number of patients to be enrolled). This sample size is sufficient to detect the risk of a 1.5-fold increase in the incidence of hypotension/blood pressure decreased and tachyarrhythmia, the adverse events with the least incidence in clinical studies (3.8%), at a two-sided significance level of 0.05 at ≥90% power.

PMDA's view:
The applicant's plan to conduct a post-marketing surveillance with the following objective is acceptable: To investigate the incidences of fluid retention, hypotension/blood pressure decreased, anaemia/haemoglobin decreased, hepatic function abnormal, teratogenicity, and tachyarrhythmia (ventricular and supraventricular arrhythmias including QT prolongation) in clinical use of clazosentan. Information on the incidence of haemorrhage intracranial should also be collected. In addition, safety information should be collected in (a) patients with moderate hepatic impairment and elderly patients aged ≥75 years (because no safety information is available in these patient populations treated with clazosentan in clinical studies) and (b) patients who receive clazosentan in combination with an OATP1B1/1B3 inhibitor, fasudil hydrochloride hydrate, or ozagrel sodium (because these drugs are likely to be co-administered with clazosentan but only limited data are available on the safety of the co-administration). Based on the above, the objective of the surveillance, the sample size, and the observation period should be discussed. PMDA will draw a final conclusion regarding the details of the post-marketing surveillance (including appropriateness of identification of safety specification and risk classification as well as appropriateness of pharmacovigilance activities and risk minimization activities), in accordance with "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2, dated April 11, 2012), 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 assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that clazosentan has efficacy in prevention of cerebrovascular spasm after surgery for aSAH and subsequent cerebral infarction and cerebral ischemic episodes, and that clazosentan has acceptable safety in view of its benefits. Clazosentan is clinically meaningful because it offers a new treatment option with a novel mechanism of action for preventing cerebrovascular spasm after surgery for aSAH and subsequent cerebral infarction and cerebral ischemic episodes. Further discussions are required on the clinical positioning of clazosentan,

indication and target population, dosage and administration, precautionary statements included in the package insert, post-marketing investigations, etc.

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

Review Report (2)

November 17, 2021

Product Submitted for Approval

Brand Name	Pivlaz I.V. Infusion Liquid 150 mg
Non-proprietary Name	Clazosentan Sodium
Applicant	Idorsia Pharmaceuticals Japan Ltd.
Date of Application	March 1, 2021

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).

1.1 Efficacy

The following results were obtained from Study 306 in patients who underwent clipping for aSAH and Study 305 in patients who underwent coiling for aSAH:

(a) The incidence of cerebrovascular spasm-associated M/M events, the primary endpoint (1), was significantly lower in the clazosentan group than in the placebo group.

(b) All-cause deaths, cerebrovascular spasm-associated new cerebral infarction, cerebrovascular spasm-associated DIND (components of the primary endpoint (1)) and moderate or severe cerebrovascular spasm (secondary endpoint) occurred less frequently in the clazosentan group than in the placebo group.

Based on these results, PMDA concluded that clazosentan was shown to have clinically significant efficacy in the prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes. This conclusion by PMDA was supported by the expert advisors.

The following comment was raised by expert advisors: Fasudil hydrochloride hydrate and ozagrel sodium are commonly available for use against post-aSAH cerebrovascular spasm in Japan, and the reasons why the Japanese phase III studies did not compare clazosentan and these conventional drugs or evaluate co-administration of clazosentan and these drugs, should be explained.

PMDA explained that the Japanese phase III studies were conducted as placebo-controlled studies for the following reasons:

(a) Clazosentan, a drug with a novel mechanism of action, was developed as a drug that can prevent the onset of cerebrovascular spasm-associated M/M events when used as a monotherapy.
(b) Conventional drugs were not evaluated for their efficacy against cerebrovascular spasm-associated M/M events before their approval, precluding the use of either of these drugs as the control drug for the phase III studies.
(c) Placebo could be used in the phase III studies by devising a study design allowing the use of conventional drugs as rescue therapy.

PMDA thus concluded that the usefulness of clazosentan for the above clinical positioning was adequately evaluated by the clinical studies. This conclusion was supported by expert advisors.

The following comment was also raised by the expert advisors:
Various pathophysiological changes in addition to cerebrovascular spasm are involved in a complicated manner in prognosis of patients after aSAH, including brain injury caused by the initial bleeding, surgical invasion, acute and subacute phase brain oedema/brain hypertension, microcirculation/venous return disorder, brain disorder caused by hematoma dissolution products (e.g., active oxygen), and disturbance of spinal fluid circulation (hydrocephalus). Accordingly, it is essential to evaluate prognosis and functional outcome.

PMDA explained that the incidence of "all-cause deaths up to Week 6 after aSAH onset," a component of the primary endpoint in Studies 306 and 305, was lower in the clazosentan group than in the placebo group [Tables 26 and 28 in Review Report (1)], and more favorable results were obtained in the clazosentan group than in the placebo group with Glasgow Outcome Scale (GOSE) (Extended version) and modified Rankin Scale (mRS), secondary endpoints in both studies that evaluate the functional outcome (Table 45). Thus, there are no tendencies of worsening in prognosis or functional outcome, demonstrating the overall efficacy of clazosentan. This conclusion by PMDA was supported by the expert advisors.

Table 45. GOSE and mRS at Week 12 after aSAH onset (FAS)

	Study AC-054-306		Study AC-054-305	
	Placebo	Clazosentan	Placebo	Clazosentan
GOSE[a]	26.4% (28/106)	18.6% (19/102)	16.5% (17/103)	10.7% (11/103)
mRS[b]	27.4% (29/106)	20.6% (21/102)	19.4% (20/103)	10.7% (11/103)

a Percentage of subjects with score 1 (death) to score 4 (upper severe disability)
b Percentage of subjects with mRS ≥3

1.2 Safety

Clazosentan is unlikely to have a risk of causing haemorrhage, judging from its pharmacological effect. In fact, there was no tendency of higher incidence of haemorrhage-related adverse events in the clazosentan group than in the placebo group either in Study 306 or in Study 305. However, because of its vasodilatory effect, clazosentan may possibly enhance haemorrhage in patients with vascular injury after invasive treatment for rupture of cerebral aneurysm; and serious intracranial haemorrhage for

which a causal relationship to clazosentan could not be ruled out occurred in the Japanese phase III studies. Taking the above into account, PMDA concluded that, in the package insert, (a) intracranial haemorrhage should be listed as a clinically significant adverse reaction, (b) clazosentan should be contraindicated in patients with intracranial haemorrhage persisting at the start of the administration, and (c) patients eligible for clazosentan therapy should be limited to those who have achieved hemostasis appropriately by surgical or endovascular treatment against ruptured cerebral aneurysm. This conclusion was supported by the expert advisors.

The following conclusion by PMDA was also supported by the expert advisors:
Since cautions are raised against haemorrhage as a clinically significant adverse reaction of fasudil hydrochloride hydrate and ozagrel sodium, the drugs approved for systemic drug therapy for cerebrovascular spasm, it is necessary to advise physicians to be careful in using these drugs in combination with clazosentan.

The following comment was raised by the expert advisors:
Antiplatelet drugs such as aspirin, clopidogrel, and cilostazol are used in patients after endovascular treatment, and are expected to be co-administered with clazosentan frequently. Information on the safety of the co-administration of clazosentan with antiplatelet agents should be provided and, at the same time, relevant information should be collected after the market launch.
PMDA instructed the applicant to appropriately provide information to healthcare professionals using information materials and to collect data through the post-marketing surveillance. The applicant responded appropriately.

The expert advisors supported PMDA's conclusions on the safety of clazosentan and necessary precautions described in Section "7.R.3 Safety" of the Review Report (1), other than those described above.

1.3 Clinical positioning and indication

The following conclusion by PMDA was supported by the expert advisors:
It is meaningful to make clazosentan available in clinical practice as a novel treatment option for the prevention of cerebrovascular spasm and associated cerebral infarction after surgery for aSAH, based on the following findings:

(a) The Japanese phase III studies demonstrated the clinically significant efficacy and acceptable safety of clazosentan.
(b) Clazosentan acts as a competitive inhibitor of endothelin receptor, a novel mechanism of action in the treatment of aSAH, and therefore has efficacy and safety profiles different from those of conventional drugs [see Sections "7.R.2 Efficacy" and "7.R.3 Safety" in Review Report (1)].

The following conclusions by PMDA were also supported by the expert advisors:
The package insert should contain statements to the effect that (a) patients eligible for treatment with clazosentan should be carefully selected based on the patient's conditions such as severity of aSAH and size of hematoma, risk of cerebrovascular spasm, and benefit-risk balance of clazosentan, and that

(b) the efficacy and safety of clazosentan have not been established in patients with WFNS grade V and patients with any Fisher grade other than grade 3.

Based on the above, PMDA has concluded that the Indication and the Precautions Concerning Indication should be as follows.

Indication
Prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes

Precautions Concerning Indication
- Whether to administer clazosentan should be decided based on the severity of subarachnoid haemorrhage, size of hematoma, the range of cerebral infarction, and other conditions of the patient. The efficacy and safety of clazosentan have not been established in the following patients:
  - Patients with World Federation of Neurosurgical Surgeons grade V
  - Patients with large territorial cerebral infarction
  - Patients other than those with Fisher grade 3
- Clazosentan should be administered to patients who have achieved hemostasis appropriately by surgical or endovascular treatment against ruptured cerebral aneurysm.

The following comment was raised by the expert advisors:
In Japan, fasudil hydrochloride hydrate and ozagrel sodium are widely available for use against post-SAH cerebrovascular spasm, whereas no data on the co-administration of these drugs with clazosentan were obtained from the Japanese phase III studies. Accordingly, healthcare professionals should be informed that the efficacy and safety of the co-administration have not been investigated, and data on the co-administration should be collected after the market launch.

PMDA instructed the applicant to disseminate information appropriately using information materials for healthcare professionals and to collect relevant information through the post-marketing surveillance. The applicant responded appropriately.

1.4 Dosage and administration

PMDA concluded that clazosentan should be administered at the speed of 10 mg/h until Day 15 after aSAH onset, the same dosage used in Studies 306 and 305, and that physicians should be advised to start administration as soon as possible, preferably but not exclusively within 48 hours after aSAH onset after examining the patient's postoperative conditions (clazosentan was to be administered within 48 hours after aSAH onset in the clinical studies). The above conclusion by PMDA was supported by the expert advisors.

The following conclusion by PMDA was also supported by the expert advisors:
(a) Clazosentan should be contraindicated in patients with severe hepatic impairment,

(b) Whether to administer clazosentan to patients with moderate hepatic impairment should be carefully assessed. If clazosentan is administered to such patients, it should be given at half the usual dose (clazosentan 5 mg/h).
(c) Co-administration of clazosentan and OATP1B1/1B3 inhibitors should be avoided except in therapeutically inevitable cases. If the co-administration of clazosentan and rifampicin, an OATP1B1/1B3 inhibitor, is unavoidable, the dose of clazosentan should be reduced to a quarter of the usual dose (i.e., 2.5 mg/h). If co-administration of clazosentan and an OATP1B1/1B3 inhibitor other than rifampicin cannot be avoided, the physician should consider reducing the dose of clazosentan and carefully monitor the clinical condition of the patient.

Based on the above, PMDA concluded that the Dosage and Administration of clazosentan and the Precautions Concerning Dosage and Administration should be as follows:

Dosage and Administration
The usual adult dosage is 300 mg (12 mL) of clazosentan diluted with 500 mL of physiological saline, continuously administered intravenously at the speed of 17 mL/h (clazosentan 10 mg/h) using a constant infusion pump. Administration of clazosentan is started early after surgery for subarachnoid haemorrhage and continued until Day 15 after the onset of subarachnoid haemorrhage. The dose may be reduced depending on the liver function and concomitant medications.

Precautions Concerning Dosage and Administration
- Administration of clazosentan should be started within 48 hours after the onset of subarachnoid haemorrhage, as a rough guide.
- Whether to administer clazosentan to patients with moderate hepatic impairment (Child-Pugh class B) should be assessed carefully and, if it is administered, the dose should be reduced to half the usual dose (clazosentan 5 mg/h). The dosage for such patients is 150 mg (6 mL) of clazosentan diluted with 500 mL of physiological saline, administered intravenously at the speed of 17 mL/h using a constant infusion pump until Day 15 after the onset of subarachnoid haemorrhage.
- Co-administration of clazosentan and rifampicin should be avoided unless therapeutically mandated. If concomitant rifampicin is administered, the dose of clazosentan should be reduced to a quarter of the usual dose (2.5 mg/h), patients should be carefully monitored, and due attention should be paid to the occurrence of adverse drug reactions. The dosage for patients receiving concomitant rifampicin is 150 mg (6 mL) of clazosentan diluted with 500 mL of physiological saline, administered intravenously at the speed of 8.5 mL/h using a constant infusion pump until Day 15 after the onset of subarachnoid haemorrhage.

1.5 Risk management plan (draft)
Based on its review presented in Section “7.R.6 Post-marketing investigations” in the Review Report (1) and on the comments raised by the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for clazosentan should include the safety specification presented in Table 46, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 47 and the use-results survey presented in Table 48.

Table 46. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Fluid retention (pleural effusion, pulmonary oedema, brain oedema) • Haemorrhage intracranial • Teratogenicity	• Hypotension/blood pressure decreased • Anaemia/haemoglobin decreased • Hepatic function abnormal • Tachyarrhythmia (ventricular and supraventricular arrhythmia including QT prolongation) • Co-administration with OATP1B1/1B3 inhibitors	• Safety in elderly patients aged ≥75 years • Safety in patients with hepatic impairment
Efficacy specification		
Not applicable		

Table 47. 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 • Use-results survey	• Disseminate information obtained from the early post-marketing phase vigilance • Organize and disseminate materials (a proper use guide for Pivlaz) for healthcare professionals

Table 48. Outline of use-results survey (draft)

Objective	To investigate the safety of clazosentan in clinical use
Survey method	Use-results survey including consecutive patients
Population	Patients receiving clazosentan after surgery for subarachnoid haemorrhage caused by cerebral aneurysm
Observation period	From the start of clazosentan administration to Week 6 after the onset of subarachnoid haemorrhage
Planned sample size	2000 (target sample size for enrollment)
Main survey items	Incidences of fluid retention, haemorrhage intracranial, hypotension/blood pressure decreased, anaemia/haemoglobin decreased, hepatic function abnormal, tachyarrhythmia, etc., patient characteristics (type of surgery for ruptured aneurysm, site, hematoma volume, Fisher grade before surgery, WFNS grade before surgery, presence/absence of large territorial cerebral infarction before the start of administration, presence/absence of cerebrovascular spasm, hepatic function, etc.), concomitant therapy, efficacy (death, new onset of cerebrovascular spasm, new onset of cerebral infarction, DIND, functional outcome [GOSE, mRS], etc.)

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

2.1 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 inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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.

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

The new drug application data (CTD 5.3.5.1.6, CTD 5.3.5.1.7) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. 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 approval 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. The drug product and its drug substance are both classified as powerful drugs.

Indication

Prevention of cerebrovascular spasm after surgery for subarachnoid haemorrhage caused by cerebral aneurysm and subsequent cerebral infarction and cerebral ischemic episodes

Dosage and Administration

The usual adult dosage is 300 mg (12 mL) of clazosentan diluted with 500 mL of physiological saline, continuously administered intravenously at the speed of 17 mL/h (clazosentan 10 mg/h) using a constant infusion pump. Administration of clazosentan is started early after surgery for subarachnoid haemorrhage and continued until Day 15 after the onset of subarachnoid haemorrhage. The dose may be reduced depending on the liver function and concomitant medications.

Approval Condition

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
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
aNIHSS	Abbreviated National Institutes of Health Stroke Scale
aSAH	Aneurysmal subarachnoid hemorrhage
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC_{0-4h}	Area under the concentration-time curve from zero to 4 hours
$AUC_{0-\infty}$	Area under the concentration-time curve from zero to infinity
AUC_{0-t}	Area under the concentration-time curve from zero to time t
AUC_{4-8h}	Area under the concentration-time curve from 4 to 8 hours
AUC_{8-12h}	Area under the concentration-time curve from 8 to 12 hours
B→A	From basolateral surface to apical surface
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSEP	Bile salt export pump
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Total body clearance
Clazosentan	Clazosentan sodium
CL_{cr}	Creatinine clearance
C_{max}	Maximum plasma concentration
COS-1	African green monkey kidney
C_{ss}	Plasma concentration at steady state
CT	Computed tomography
CYP	Cytochrome P450
DIND	Delayed Ischemic Neurological Deficit
DMSO	Dimethyl sulfoxide
DSA	Digital subtraction angiography
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
ET	Endothelin
ET-1	Endothelin-1
ET_A	Endothelin A receptor
ET_B	Endothelin B receptor
FAS	Full analysis set
f_u	Fraction unbound
GC	Gas chromatography
GOSE	Glasgow Outcome Scale (Extended version)
HEK	Human embryonic kidney
hERG	Human ether a-go-go related gene
HLGT	High level group terms
HPLC	High performance liquid chromatography
HPTLC	high performance thin layer chromatography
IC_{50}	Half maximal inhibitory concentration
ICH Q1E Guidelines	“Guidelines on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3B Guidelines	“Revision of the Guidelines on Impurities in New Drug Products” (PFSB/ELD Notification No. 0703004 dated July 3, 2006)
ID_{50}	Dose that causes 50% inhibition

IR	Infrared absorption spectroscopy
K_i	Inhibition constant
K_m	Michaelis-Menten constant
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
MAP	Mean arterial blood pressure
MATE	Multidrug and toxin extrusion
MDCK II	Madin-Darby canine kidney strain II
MedDRA	Medical Dictionary for Regulatory Activities
mGCS	Modified Glasgow Coma Scale
MPS-chloride	4-(4-chloro-5-(2-methoxyphenoxy)-6-((5-methylpyridine)-2-sulfonamido) pyrimidin-2-yl)pyridine 1-oxide
MPS-hydroxyether sodium	4-(4-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-6-((5-methylpyridine)-2-sulfonamido)pyrimidin-2-yl)pyridine 1-oxide sodium
MPS-nitrile	N-(2-(2-cyanopyridin-4-yl)-6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy) pyrimidin-4-yl)-5-methylpyridine-2-sulfonamide
mRNA	Messenger ribonucleic acid
MRP	Multidrug resistance-associated protein
mRS	modified Rankin Scale
MS	Mass spectrometry
MTD	Maximum tolerated dose
NIHSS	National Institutes of Health Stroke Scale
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
pA_2	Negative logarithm of the molar concentration of antagonist that causes a 2-fold shift to the right of an agonist concentration-response curve
PAH	Pulmonary arterial hypertension
P_{app}	Apparent permeability coefficient
P-gp	P-glycoprotein
Pivlaz	Pivlaz for I.V. Infusion
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PPS	Per Protocol Set
PT	Preferred terms
QTcF	Fridericia-corrected QT Interval
RH	Relative humidity
SAH	Subarachnoid hemorrhage
SD	Sprague-Dawley
SMQ	Standardised MedDRA queries
SRTX	Sarafotoxin
Study 305	Study AC-054-305
Study 306	Study AC-054-306
$t_{1/2}$	Elimination half-life
t_{max}	Time of maximum plasma concentration
UV	Ultraviolet spectroscopy
V_{ss}	Volume of distribution at steady state
WFNS	World Federation of Neurosurgical Surgeons
γ-GTP	γ-glutamyl transpeptidase