Report on the Deliberation Results

March 3, 2020

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

Brand Name	Steboronine 9000 mg/300 mL for Infusion
Non-proprietary Name	Borofalan (^{10}B) (JAN*)
Applicant	Stella Pharma Corporation
Date of Application	October 15, 2019

Results of Deliberation

In its meeting held on February 26, 2020, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

2. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

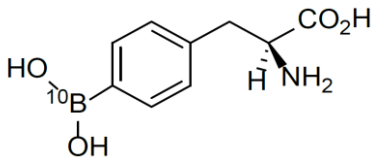
Review Report

February 6, 2020
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	Steboronine 9000 mg/300 mL for Infusion
Non-proprietary Name	Borofalan (^{10}B)
Applicant	Stella Pharma Corporation
Date of Application	October 15, 2019
Dosage Form/Strength	An injectable solution containing 9000 mg of borofalan (^{10}B) per bag (300 mL)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_9H_{12}{}^{10}BNO_4$

Molecular weight: 208.21

Chemical name: (*S*)-2-Amino-3-[4-(^{10}B)dihydroxyboranylphenyl]propanoic acid

Items Warranting Special Mention

SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 4 of 2017 [*29-yaku*]; PSEHB/PED Notification No. 0421-1, dated April 21, 2017, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that boron neutron capture therapy using the product has a certain level of efficacy in the treatment of patients with unresectable, locally advanced or locally recurrent head and neck cancer, 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 conditions. Dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, carotid haemorrhage, and late toxicity need to be further investigated.

Indication

Unresectable, locally advanced or locally recurrent head and neck cancer

Dosage and Administration

Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h.

Approval Conditions

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

2. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

December 27, 2019

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	Steboronine 9000 mg/300 mL for Infusion
Non-proprietary Name	Borofalan (^{10}B)
Applicant	Stella Pharma Corporation
Date of Application	October 15, 2019
Dosage Form/Strength	An injectable solution containing 9000 mg of borofalan (^{10}B) per bag (300 mL)
Proposed Indications	Unresectable locally recurrent head and neck cancer Unresectable advanced head and neck non-squamous cell carcinoma

Proposed Dosage and Administration

Usually, for adults, a single dose of 500 mg/kg of borofalan (^{10}B) is administered as an intravenous infusion over 3 hours, at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during the last 1 hour. Irradiation of neutron beams to the cancer area is started at 2 hours after the start of intravenous infusion. The intravenous infusion is terminated at the end of irradiation. (In a patient weighing 60 kg, 800 mL of Steboronine solution is intravenously infused over 2 hours, followed by intravenous infusion of 200 mL over 1 hour.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

In boron neutron capture therapy (BNCT), neutron beam is irradiated from outside the body to tumor cells that have incorporated ^{10}B. The irradiated ^{10}B releases alpha rays and lithium nuclei, resulting in cytocidal effects.

Steboronine, discovered by the applicant, is a drug with an increased abundance ratio of ^{10}B in boron atom contained in 4-borono-L-phenylalanine, a phenylalanine derivative.

1.2 Development history etc.

In Japan, a phase I study (Study WW2P2040E001/SPM-011-JHN001 [Study 001]) was initiated in March 2014 by the applicant and Sumitomo Heavy Industries, Ltd., involving patients with unresectable locally recurrent head and neck squamous cell carcinoma or unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma. Subsequently, a phase II study (Study WW2P2040E004/SPM-011-JHN002 [Study 002]) was initiated in June 2016 by the applicant and Sumitomo Heavy Industries, Ltd., involving (a) patients with post-chemoradiotherapy (CRT) or post-radiotherapy (RT) unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma. As of November 2019, borofalan is not approved in any country or region.

Borofalan is designated as a SAKIGAKE product (SAKIGAKE Drug Designation No. 4 of 2017 [*29-yaku*]) in April 2017 with the intended indication of "unresectable locally recurrent head and neck cancer and unresectable advanced head and neck cancer (non-squamous cell carcinoma).

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is white crystals or crystalline powder. The general properties of the drug substance, including description, solubility, hygroscopicity, melting point, thermal analysis, dissociation constant, and distribution coefficient have been determined.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry, ultraviolet/visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (NMR; ^{1}H-NMR, ^{13}C-NMR), and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] as the starting material.

The processes of hydrolysis/decarboxylation, [redacted], and [redacted] have been defined as critical steps, and in-process control parameters and control values have been established for each of the steps. [redacted] is controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV/VIS and IR), purity (clarity and color of solution, chloride, heavy metals, arsenic, related substances [liquid chromatography (LC)], optical isomers [LC]), residual solvents (gas chromatography [GC]), and ^{10}B abundance ratio (inductively coupled plasma mass spectrometry), loss on drying, [redacted], and assay (LC).

2.1.4 Stability of drug substance

Table 1 shows stability studies conducted on the drug substance. 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 testing	3 pilot scale batches	25°C	60% RH	Double-layered low-density polyethylene bag + fiber drum	60 months
Accelerated testing		40°C	75% RH		6 months

Based on the above, a retest period of 60 months has been proposed for the drug substance when stored at room temperature in the double-layered low-density polyethylene bag placed in a fiber drum.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection containing 9 g of the drug substance in each soft bag (300 mL). The drug product contains excipients: D-sorbitol, sodium hydrogen sulfite, sodium hydroxide, hydrochloric acid, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through the following processes: Acceptance test, dissolution, pH and volume adjustment, sterile filtration, filling/sealing, [redacted], and labeling/packaging.

Critical processes are pH and volume adjustment, sterile filtration, filling/sealing, and [redacted]. In-process control parameters and control values have been established for the processes of dissolution, pH and volume adjustment, sterile filtration, filling/sealing, and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (ninhydrin reaction, borate, and UV spectroscopy), osmotic pressure ratio, pH, purity (related substances [LC] and optical isomers [LC]), bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay (LC).

2.2.4 Stability of drug product

Table 2 shows the stability studies conducted on the drug product. A photostability test showed that the drug product was photolabile.

Table 2. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot scale batches	5°C	-	Polybutadiene rubber cap + low-density polyethylene soft bag + pillow bag containing an iron-based oxygen absorber	[redacted] months
Accelerated testing		25°C	60% RH		6 months

-, Not adjusted.

Based on the above, the shelf life of 36 months has been proposed for the drug product when stored protected from light at 2°C to 8°C in polybutadiene cap-sealed low-density polyethylene soft bags placed in a pillow bag containing an iron-based oxygen absorber.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following reviews, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.R.1 Novel excipient

The drug product contains D-sorbitol, a novel excipient, in an amount exceeding that contained in the existing products for intravenous injection.

2.R.1.1 Specifications and stability

D-sorbitol conforms to the Japanese Pharmacopoeia (JP). PMDA concluded that there were no problems with the specifications and stability.

2.R.1.2 Safety

As a result of reviewing the data submitted, PMDA concluded that D-sorbitol at the proposed content is unlikely to raise any safety concern.

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

3.1 Primary pharmacodynamics

3.1.1 Growth-inhibitory effect on malignant tumor-derived cell lines

3.1.1.1 *In vitro* (CTD 4.2.1.1-1)

A colony forming assay was conducted to investigate the growth inhibitory effect of BNCT with borofalan (borofalan/BNCT; neutron beam irradiation dose 1.54, 3.08, 4.62, and 6.16 × 10^{11} n/cm^2) against human tongue cancer-derived SAS cell line, human glioblastoma-derived U-87MG cell line, mouse squamous cell carcinoma-derived SCCVII cell line, and human normal fibroblast-derived NB1RGB cell line. Borofalan/BNCT inhibited the growth of all cell lines tested.

3.1.1.2 *In vivo* (CTD 4.2.1.1-2 and 4.2.1.1-3)

The tumor growth-inhibitory effect of borofalan/BNCT was investigated using nude mice subcutaneously transplanted with SAS cell line (n = 8 or 10/group). The day when tumor volume

reached 1 to 2 mm^3 was defined as the study initiation date (Day 0). On Day 0, borofalan (500 mg/kg) was administered intravenously to mice, followed by irradiation of neutron beam (skin dose 4 gray equivalent [Gy-Eq.]) and, on Day 22, tumor volume was calculated. A statistically significant inhibition of tumor growth was observed in the borofalan/BNCT group compared with the control groups (untreated group and neutron beam irradiation group) ($P < 0.0001$ against both control groups, Tukey's test).

The tumor growth-inhibitory effect of borofalan/BNCT was investigated using nude mice subcutaneously transplanted with U-87MG cell line (n = 9 or 10/group). The day when tumor volume reached 1 to 2 mm^3 was defined as the study initiation date (Day 0). On Day 0, borofalan (500 mg/kg) was administered intravenously to mice, followed by irradiation of neutron beams (skin dose, 4 Gy-Eq.) and, on Days 21, 28, and 35, tumor volume was calculated. A statistically significant inhibition of tumor growth was observed in the borofalan/BNCT group compared with the control groups (untreated group and neutron beam irradiation group) (Figure 1).

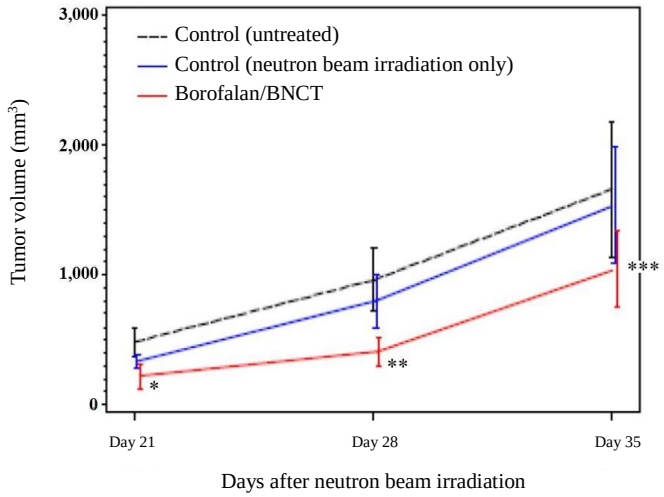


Figure 1. Tumor growth-inhibitory effect of borofalan/BNCT in nude mice subcutaneously transplanted with U-87MG cell line

n = 9 or 10;
* $P < 0.05$ against the untreated group
** $P < 0.0001$ and $P < 0.01$, respectively, against the untreated group and the neutron beam irradiation group
*** $P < 0.0001$ and $P < 0.001$, respectively, against the untreated group and the neutron beam irradiation group
Repeated-measure analysis of variance

3.2 Safety pharmacology

3.2.1 Effect on the central nervous system (CTD 4.2.1.3-1)

A single dose of borofalan (250, 500, or 1,000 mg/kg) was administered intravenously to rats (n = 6/group), and the effect of borofalan on clinical signs and behavior was investigated by the modified Irwin method. Borofalan had no effect either on clinical signs or behavior.

3.2.2 Effect on the cardiovascular system

3.2.2.1 Effect on hERG potassium current (CTD 4.2.1.3-3)

The effect of borofalan (0.05, 0.5, or 5 mg/mL) on human *ether-a-go-go*-related gene (hERG) potassium current was investigated using human embryonic kidney-derived HEK293 cell line

transfected with hERG. The inhibition rate (mean ± standard error, n = 5) of hERG potassium current in the borofalan 0.05, 0.5, and 5 mg/mL groups relative to the control[1)] group was −2.6% ± 8.5%, −0.7% ± 5.2%, and −2.0% ± 7.0%, respectively.

3.2.2.2 Effect on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3-4)

A single dose of borofalan (250, 500, and 1,000 mg/kg) was sequentially administered intravenously to dogs (n = 4), and the effect on blood pressure (systolic, diastolic, and mean), heart rate, and electrocardiogram (PQ interval, QRS complex duration, QT interval, and QT interval corrected [QTc]) was investigated until 24 hours after treatment with borofalan. A statistically significant decrease in heart rate was observed in the borofalan 250 and 500 mg groups compared with the control (31.5 mg/mL D-sorbitol) group.[2)] A statistically significant prolongation of QT interval was observed in all borofalan groups compared with the control (31.5 mg/mL D-sorbitol) group.[3)]

The applicant's explanation:
In clinical use, borofalan is unlikely to pose any safety problem regarding QT interval prolongation, judging from the following observations:

- QTc prolongation was not observed in any borofalan group, and QT interval prolongation and decreased heart rate were observed simultaneously after administration of borofalan at 250 and 500 mg/kg. This suggests that the QT interval prolongation was a transient change associated with the decreased heart rate.

- The estimated C_{max} (1,260-1,900 μg/mL) of unbound borofalan in plasma in dogs receiving borofalan 1,000 mg/kg was higher than C_{max} (812 μg/mL)[4)] of unbound borofalan in plasma in humans receiving the recommended clinical dose (500 mg/kg).

3.2.3 Effect on respiratory system (CTD 4.2.1.3-2)

A single dose of borofalan (250, 500, or 1,000 mg/kg) was administered intravenously to rats (n = 6/group), and the effect of borofalan on the respiratory function (respiratory rate, tidal volume, and minute ventilation volume) was investigated. No effect of borofalan was observed.

3.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following section, PMDA concluded that the applicant's discussions on the nonclinical pharmacology of borofalan are acceptable.

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1) To prepare the control solution, 31.5 mg/mL D-sorbitol solution was diluted 1:6 with extracellular solution (134.4 mmol/L sodium chloride, 4.8 mmol/L potassium chloride, 2.16 mmol/L calcium chloride dihydride, 1.2 mmol/L magnesium chloride hexahydride, 12.0 mmol/L HEPES, and 12.0 mmol/L glucose).

2) 0 and 1 hour after the end of borofalan treatment in the borofalan 250 mg/kg group ($P < 0.01$ and $P < 0.05$, respectively, against the control group); 0.5 and 1 hour after the end of borofalan treatment in the borofalan 500 mg/kg group (both $P < 0.05$ against the control group) (Dunnett's multiple comparison).

3) 0, 1, and 2 hours after the end of borofalan treatment in the borofalan 250 mg/kg group ($P < 0.05$, $P < 0.05$, and $P < 0.01$, respectively, against the control group); 0.5, 1, and 2 hours after the end of borofalan treatment in the borofalan 500 mg/kg group (both $P < 0.05$ against the control group); 0 hour after the end of borofalan treatment in the borofalan 1,000 mg/kg group ($P < 0.05$ against the control group) (Dunnett's multiple comparison).

4) C_{max} following a single intravenous administration of borofalan (500 mg/kg) to Japanese patients with unresectable head and neck cancer in Study 001 [see Section 6.2.1.1].

3.R.1 Mechanism of action and efficacy of borofalan/BNCT

The applicant's explanation about the mechanism of action of borofalan/BNCT and the efficacy for head and neck cancer:

Borofalan is a boron compound, namely phenylalanine labeled with ^{10}B (an isotope of boron). Phenylalanine is an amino acid essential for the growth of tumor cells (*J Am Chem Soc*. 1958;80:835-8). It has been suggested that the compound accumulates in tumor cells, mediated by L-type amino acid transporter-1 (LAT-1) (*Membrane*. 2008;33:108-17), an amino acid transporter highly expressed in multiple types of carcinomas including head and neck cancer (*Cancer Res*. 2009;69:2126-32).

Borofalan alone does not inhibit tumor growth, whereas upon irradiation of neutron beams from outside the body, ^{10}B atoms incorporated in tumor cells capture neutrons, resulting in the release of alpha rays and lithium nuclei generated by nuclear reaction, exhibiting a tumor growth-inhibitory effect (*Int J Radiat Biol*. 2006;82:21-9).

The efficacy of borofalan/BNCT is suggested by this mechanism of action and by the fact that borofalan/BNCT showed tumor growth-inhibitory effect in nude mice subcutaneously transplanted with a human head and neck carcinoma cell line. [see Section 3.1.1].

PMDA accepted the applicant's explanation.

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

The pharmacokinetics (PK) of borofalan was investigated in mice, rats, and dogs. Plasma protein binding of borofalan, drug-metabolizing enzymes, and transporters were investigated using biomaterials of human and animal origins.

4.1 Absorption

A single dose of ^{14}C-labeled borofalan (500 mg/kg) was administered intravenously to male dogs, and plasma radioactivity was investigated. Table 3 shows PK parameters of radioactivity observed.

Table 3. PK parameters of radioactivity (male dogs, single intravenous administration)

N	C_{max} (mg Eq./mL)	AUC_{inf} (mg Eq. ·h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	Vd_{ss} (L/kg)
3	1.39 ± 0.042	6.59 ± 1.01	55 ± 17	0.07 ± 0.01	2.5 ± 0.46

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled borofalan (125 or 500 mg/kg) was administered intravenously to male nude mice subcutaneously transplanted with U-87MG cell line, and tissue distribution of radioactivity was investigated. No clear difference was observed in the tissue distribution of radioactivity between the 125 mg/kg group and the 500 mg/kg group. In the 500 mg/kg group, the radioactivity was distributed over various tissues, and tissue radioactivity concentration reached the maximum level within 15 minutes after the end of treatment in most of the tissues including plasma and blood. The radioactivity concentration at 15 minutes after the end of treatment was particularly high in pancreas

and kidney (3.06 and 1.90 mg Eq./g, respectively) compared with the concentration in plasma and blood (0.292 and 0.355 mg Eq./mL, respectively). The radioactivity concentration (range) from 15 minutes to 2 hours after the end of treatment was higher in tumor (0.352-0.388 mg Eq./g) than in plasma and blood (0.141-0.292 and 0.162-0.355 mg Eq./mL, respectively), and radioactivity was eliminated from tumor more gradually than from plasma and blood.

A single dose of ^{14}C-labeled borofalan (500 mg/kg) was administered intravenously to male albino rats, and tissue distribution of radioactivity was investigated. The tissue distribution rate of radioactivity (percentage of the administered radioactivity) at 1 hour after the end of treatment was particularly higher in skeletal muscles and skin (39% and 15%, respectively) than in plasma and blood (1.5% and 2.9%, respectively). The tissue distribution rate of radioactivity at 168 hours after the end of treatment was ≤0.1% in most of the tissues, but 2.6% and 1.3%, respectively, in skeletal muscles and skin.

A single dose of ^{14}C-labeled L-phenylalanine (500 mg/kg) was administered intravenously to male albino rats, and tissue distribution of the radioactivity was investigated. The radioactivity was distributed widely in various tissues, and radioactivity concentration in most of the tissues including plasma and blood reached the maximum level within 1 hour after the end of treatment. The radioactivity at 1 hour after the end of treatment was particularly higher in the pancreas (2.28 mg Eq./g) than in plasma and blood (0.394 and 0.288 mg Eq./mL, respectively). The tissue distribution rate at 1 hour after the end of treatment was particularly higher in skeletal muscles and skin (30% and 15%, respectively) than in plasma and blood (2.3% and 3.2%, respectively). The tissue distribution rate at 168 hours after the end of treatment was ≤0.1% in most of the tissues, but 16% and 6%, respectively, in skeletal muscles and skin.

Based on the above results, the applicant explained that borofalan shows a tissue distribution similar to that of L-phenylalanine.

4.2.2 Plasma protein binding

Plasma samples of rats, dogs, and humans were incubated with ^{14}C-labeled borofalan (10, 100, or 1,000 μg/mL) at 37°C for 15 minutes, and plasma protein binding of borofalan was investigated by ultracentrifugation. Plasma protein binding rate of borofalan was 0% to 10% in rats, 2% to 17% in dogs, and 0% to 22% in humans.

Human serum albumin (40 mg/mL), human immunoglobulin (Ig)G (20 mg/mL), or human α1-acid glycoprotein (0.5 mg/mL) was incubated with ^{14}C-labeled borofalan (10, 100, or 1,000 μg/mL) at 37°C for 15 minutes, and the binding of borofalan to human serum albumin, human IgG, and human α1-acid glycoprotein was investigated by ultracentrifugation. The binding rate of borofalan to human serum albumin, human IgG, and human α1-acid glycoprotein was 5.4% to 17%, 5.4% to 9.0%, and 4.3% to 7.7%, respectively.

4.2.3 Distribution in blood cells

Blood samples of rats, dogs, and humans were incubated with ^{14}C-labeled borofalan (10, 100, or 1,000 μg/mL) at 37°C for 15 minutes, and distribution of borofalan in blood cells was investigated.

The distribution rate of borofalan in blood cells was 14% to 43% in rats, 0% to 2% in dogs, and 1% to 9% in humans. The applicant explained that these results suggest that borofalan is distributed mainly in plasma.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of borofalan was not investigated. The applicant explained that borofalan may cross the placenta into the fetus, judging from the molecular weight of borofalan (208.21) and its plasma protein binding rate [see Section 4.2.2].

4.3 Metabolism

4.3.1 *In vitro*

^{14}C-labeled borofalan (50 μmol/L) was incubated at 37℃ for 2 hours (a) with S9 fraction of rat, dog, or human liver or (b) without liver S9 fraction, and metabolism of borofalan was investigated. The residual rate of borofalan was (a) 88.6%, 87.7%, and 84.1%, and (b) 80.4%, respectively, and L-tyrosine was the only compound detected other than borofalan. Based on the above results, the applicant explained that borofalan is metabolized to L-tyrosine, but not by enzymes of liver S9 fractions.

4.3.2 *In vivo*

A single dose of ^{14}C-labeled borofalan (500 mg/kg) was administered intravenously to male rats, and its metabolites in plasma, urine, and feces were investigated. The following results were obtained:

- Mainly the unchanged borofalan was detected in the plasma at 8 hours after the end of treatment (percentage relative to the total radioactivity in plasma, 92%).

- Mainly the unchanged borofalan and M7 (phenylpyruvate form) were detected in the urine collected up to 24 hours after the end of treatment (percentage of the administered radioactivity, 25% and 18%, respectively).

- Mainly the unchanged borofalan and M9 (hydroxyphenyllactate form) were detected in the feces collected up to 24 hours after the end of treatment (percentage of the administered radioactivity, 1% each for both compounds).

4.4 Excretion

4.4.1 Excretion in urine, feces, and expired air

A single dose of ^{14}C-labeled borofalan (500 mg/kg) was administered intravenously to male rats, and excretion rates (percentages of the administered radioactivity) of the radioactivity in urine, feces, and expired air were investigated. The excretion rates in urine, feces, and expired air up to 168 hours after the end of treatment were 77%, 8%, and 8%, respectively. According to the applicant, these results suggest that borofalan is excreted mainly in urine.

4.4.2 Excretion in milk

Borofalan excretion in milk was not investigated. The applicant explained that borofalan may be excreted in milk, judging from its molecular weight (208.21) and plasma protein binding rate [see Section 4.2.2].

4.5 Pharmacokinetic interactions

4.5.1 Transporters

The applicant's explanation about pharmacokinetic interactions of borofalan mediated by transporters:
Results of the following studies showed that borofalan is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, or MATE2-K:

- P-gp-mediated transport of ^{14}C-labeled borofalan (5 μmol/L) was investigated using porcine renal epithelial cell-derived LLC-PK1 cell line expressing human P-gp. The ratio of efflux ratio[5)] of ^{14}C-labeled borofalan was 0.8.

- BCRP-mediated transport of ^{14}C-labeled borofalan (5 μmol/L) was investigated using membrane vesicles expressing human BCRP. ^{14}C-labeled borofalan uptake activity in the presence of adenosine monophosphate (AMP) was not clearly different from the activity in the presence of adenosine triphosphate (ATP).

- ^{14}C-labeled borofalan (5 μmol/L) transport mediated by human OAT1, OAT3, OCT2, MATE1, or MATE2-K was investigated using HEK293 cell line expressing these transporters. ^{14}C-labeled borofalan uptake activity of each cell line expressing any of these transporters was not clearly different from that of the cell line not expressing these transporters.

The applicant explained the pharmacokinetic interactions due to inhibition of the following transporters by borofalan: (a) P-gp and BCRP and (b) organic anion transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

The applicant's explanation:

- The inhibitory effect of borofalan (1-100 μmol/L) against the transport of each substrate[6)] mediated by P-gp and BCRP was investigated using LLC-PK1 cell line expressing human P-gp or BCRP. The ratio of efflux ratio[5)] of the substrates of P-gp and BCRP did not show clear decrease with the increase in borofalan concentration. These results suggest that, in clinical use, borofalan is unlikely to cause pharmacokinetic interactions through inhibition of P-gp or BCRP.

- The inhibitory effect of borofalan (1-100 μmol/L) against the transport of substrates[7)] mediated by human OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K was investigated using HEK293 cell line expressing these transporters. Borofalan did not show a clear inhibitory

5) The ratio of efflux ratio in transporter-expressing cells to efflux ratio in cells not expressing transporters
6) ^{3}H-labeled digoxin (1 μmol/L) and ^{3}H-labeled prazosin (0.01 μmol/L) were used as substrates of P-gp and BCRP, respectively.
7) The following substrates were used: ^{3}H-labeled *p*-aminohippuric acid (1 μmol/L) for OAT1, ^{3}H-labeled ammonium estrone sulfate (0.05 μmol/L) for OAT3, ^{3}H-labeled estradiol-17β-glucuronide (0.05 μmol/L) for OATP1B1 and OATP1B3, and ^{14}C-labeled metformin (10 μmol/L) for OCT2, MATE1, and MATE2-K.

effect against the intracellular uptake of these substrates. However, borofalan concentrations used in these studies were lower than the C_{max} in humans receiving borofalan at the proposed dosage and administration [see Section 6.2.1.1]. Therefore, in clinical use, borofalan may have the potential to cause pharmacokinetic interactions by inhibiting OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

4.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following section, PMDA concluded that the applicant's discussions on the nonclinical pharmacokinetics of borofalan are acceptable.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about pharmacokinetic interactions due to inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K by borofalan [see Section 4.5.1]:

In the Japanese phase II study (Study 002), only a limited number of patients received borofalan in combination with the substrates of these transporters, but they did not show any particular safety problems. Based on this finding and other information available currently, coadministration of borofalan and substrates of the transporters is unlikely to pose any problem clinically.

PMDA's view:

The applicant's explanation is generally acceptable. However, since information on the pharmacokinetic interactions of borofalan mediated by OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K is important for the proper use of borofalan, the relevant information should be collected continuously and provided appropriately to healthcare professionals when useful information become available.

5. Toxicity and Outline of the Review Conducted by PMDA

Vehicles used in this section were 31.5 mg/mL D-sorbitol solution for *in vivo* studies and dimethyl sulfoxide (DMSO) for *in vitro* studies, unless specified otherwise.

5.1 Single-dose toxicity

Single intravenous dose toxicity studies were conducted in rats and dogs to evaluate acute toxicity. The approximate lethal dose of borofalan was >1,000 mg/kg in both animal species (Table 4).

Table 4. Single-dose toxicity studies (borofalan)

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (Sprague Dawley)	i.v.	0, 0,[a] 250, 500, 1,000	1,000: Chromaturia	>1,000	4.2.3.1.1
Male and female rats (Sprague Dawley)	i.v.	0, 500, 1,000	≥500: Loss of direct light reflex due to miosis, and submandibular acinar cell hypertrophy 1,000: Mammary gland lobule hyperplasia, corpus luteum hypertrophy, and mucus degeneration of vaginal mucosal epithelium	>1,000	4.2.3.1.2[b]
Male dogs (beagle)	i.v.	0, 250, 500, 1,000	1,000: Precipitates in urinary sediment supposedly consisting of borofalan	>1,000	4.2.3.1.3
Male and female dogs (beagle)	i.v.	0, 250, 500, 1,000	≥500: Miosis	>1,000	4.2.3.1.4[c]

a) Only physiological saline was administered.
b) Acute toxicity was evaluated in mammary gland, female reproductive organs, liver, and submandibular gland, because these organs showed histopathological changes in the 2-week repeated intravenous dose toxicity study in rats [see Section 5.2].
c) Acute toxicity was evaluated in the eye because toxicity findings were observed in the eye in the 2-week repeated intravenous dose toxicity study in dogs [see Section 5.2].

Mice were given a subcutaneous administration[8)] of borofalan, and then their heads were irradiated with a single dose of neutron beams for 30 or 40 minutes. Acute phase toxicity (necropsied on Days 4, 8, 15, and 29 after irradiation) and long-term toxicity (necropsied on Days 90, 150, and 180 after irradiation) were evaluated. The approximate lethal dose of borofalan was 1,000 mg/kg in males and >1,000 mg/kg in females in the group receiving neutron beam irradiation for 30 minutes, and 500 mg/kg in males and 1,000 mg/kg in females in the group receiving neutron beam irradiation for 40 minutes (Table 5). Main toxicities observed included weight loss, decreases in food and water consumption, changes in hematopoietic and immunological organs, degeneration and necrosis of lingual mucosal epithelium, changes in male and female reproductive organs, and cataract. Death occurred during the early phase (Days 10-14 after irradiation) and during the late phase (Days 51-94 after irradiation). The assumed causes of early-phase death were (a) eating disorder due to the degeneration and necrosis of lingual mucosal epithelium and (b) the deterioration of systemic conditions due to immune suppression. The assumed cause of late-phase death was deterioration of systemic conditions due to immune suppression. In the preliminary study for this study, borofalan (1,000 mg/kg) was administered subcutaneously to mice, followed by neutron beam irradiation for 40 minutes; the exposure dose in the skin and brain of the mice (corresponding to approximately 12 and 9 Gy-Eq., respectively) was approximately 1.3 and 4 times, respectively, the maximum estimated exposure dose in the skin (9 Gy-Eq.) and brain (2.25 Gy-Eq.) of humans receiving borofalan/BNCT.

8) Subcutaneous administration was used because this administration route results in PK similar to that in humans receiving a single intravenous administration of borofalan.

Table 5. Single dose toxicity study (borofalan/BNCT)

Test system	Route of administration	Dose (mg/kg)[a)]	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Acute phase toxicity Male and female mice (BALB/c)	s.c.	0, 500, 1,000	Death[b)]: 500 (40-minute neutron beam irradiation: 2 of 18 males), 1,000 (30-minute neutron beam irradiation: 1 of 24 males), 1,000 (40-minute neutron beam irradiation: 7 of 24 males, 3 of 24 females), decreased activity, hunchback position, eye discharge, lid closure, decreases in body weight/food consumption/water consumption, decreased hematopoietic cells in sternal/femoral bone marrow, atrophy of thymus/spleen/submandibular lymph nodes, degeneration/necrosis of lingual mucosal epithelium, atrophy of ovarian/uterine/vaginal mucosal epithelia, etc. Changes observed at 0 (40-minute neutron beam irradiation): Decreases in body weight/food consumption/water consumption, decreases in platelet/white blood cell/lymphocyte/neutrophil/monocyte/eosinophil counts, increased bilirubin, decreases in thymic/splenic/testicular weights, decreases in hematopoietic cells in sternal/femoral bone marrow, atrophy of thymus/spleen/submandibular lymph node/mesenteric lymph node/Peyer's patch, regeneration of mucosal epithelium of small/large intestinal crypts, inhibition of spermatogenesis, etc. Changes observed at 500 or 1,000 (30- or 40-minute neutron beam irradiation): Decreases in body weight/food consumption/water consumption, effect on lymphatic/hematopoietic/gastrointestinal systems, degeneration/necrosis of lingual mucosal epithelium, atrophy of ovarian/uterine/vaginal mucosal epithelia, inhibition of spermatogenesis, cataract, etc.	30-minute irradiation Male: 1,000 Female: >1,000 40-minute irradiation Male: 500 Female: 1,000	4.2.3.1.7 (reference)
Long-term toxicity Male and female mice (BALB/c)	s.c.	0, 500, 1,000	Death[c)]: 500 (40-minute neutron beam irradiation: 9 of 18 males), 1,000 (30-minute neutron beam irradiation: 13 of 18 males, 1 of 18 females), 1,000 (40-minute neutron beam irradiation: 34 of 36 males, 28 of 36 females), eye discharge, lid closure, hunchback position, reduced body weight gain, decreases in food/water consumption, decreased hematopoietic cells in sternal/femoral bone marrow, atrophy of thymus/spleen/lymph nodes, degeneration/necrosis of lingual mucosal epithelium, atrophy of ovarian/uterine/vaginal mucosal epithelia, decreased pancreatic zymogen granules, etc. Changes observed at 0 (40-minute neutron beam irradiation): Increased total plasma cholesterol, decreased plasma amylase activity, decreased weight of submandibular gland/thymus/spleen/testis/ovary/uterus, cataract, atrophy of testicular seminiferous tubules, atrophy of ovarian/uterine/vaginal mucosal epithelia, decreased follicular count, mucus degeneration of vaginal mucous membrane, etc. Changes observed at 500 or 1,000 (30-or 40-minute neutron beam irradiation): Eye discharge, lid closure, hunchback position, reduced body weight gain, decreases in food/water consumption, increased total plasma cholesterol, decreases in plasma triglycerides/amylase activities, ocular white turbidity, small uterus, decreased weight of submandibular gland/thymus/spleen/testis/ovary/uterus/heart/kidney/liver, cataract, atrophy of testicular seminiferous tubules, atrophy of ovarian/uterine/vaginal mucosal epithelia, decreased follicular count, mucus degeneration of vaginal mucous membrane, etc.	30-minute irradiation Male: 1,000 Female: >1,000 40-minute irradiation Male: 500 Female: 1,000	4.2.3.1.8 (reference)

a) Following a subcutaneous administration of borofalan or vehicle, the head of animals was irradiated with a single dose of neutron beams (30 or 40 minutes in the borofalan group, 0 or 40 minutes in the vehicle group). The day of administration of borofalan was counted as Day 1. Animals were necropsied on Days 4, 8, 15, and 29 for evaluation of acute phase toxicity and on Days 90, 150, and 180 for evaluation of long-term toxicity.
b) Death was observed 10 to 12 days after neutron beam irradiation.
c) Death was observed 10 to 14 days and 51 to 94 days after neutron beam irradiation.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies (2 and 4 weeks) of borofalan were conducted in rats and dogs (Table 6). Main toxicities observed included light reflex lost, changes in mammary gland and male and female reproductive organs, changes in kidney (including abnormal test values), and change of submandibular gland in rats; and corneal opacity, light reflex lost, miosis, drowsiness, tremor, relaxation of nictating membrane, and changes in female reproductive organs in dogs.

In the 4-week repeated-dose toxicity studies in rats and dogs, the exposure to borofalan (C_{max} and $AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAEL) [(a) <125 mg/kg/day in rats, (b) 125 mg/kg/day in male dogs, (c) <125 mg/kg/day in female dogs] was (a) <196.4 μg/mL and <904.3 μg·h/mL, (b) 207.1 μg/mL and 1507 μg·h/mL, and (c) <269.3 μg/mL and <1518 μg·h/mL, respectively, which were (a) <0.24 times and <0.15 times (b) 0.26 times and 0.26 times, and (c) <0.33 times and <0.26 times the clinical exposure,[9)] respectively.

[9)] In Study 001, C_{max} and AUC_{inf} following a single intravenous administration of borofalan (500 mg/kg) was 812 μg/mL and 5,811 μg·h/mL, respectively [see Section 6.2.1.1].

Table 6. Repeated-dose toxicity studies (borofalan)

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	i.v.	2-week treatment (QD) + 2-week withdrawal	0,[a] 0, 250, 500, 1,000	Death: 500 (1 of 10 males) ≥250: Chromaturia, mammary gland lobule hyperplasia, corpus luteum hypertrophy, mucus degeneration of vaginal mucosal epithelium, endometrial hyperplasia, hypertrophy of submandibular acinar cells ≥500: Light reflex lost, decreased serum inorganic phosphorus, decreases in urine osmotic pressure/specific gravity 1,000: Inanimation, decreases in body weight/food consumption, decreased reticulocyte rate, increased neutrophil ratio, decreased serum alkaline phosphatase, decreased weight of uterus/liver/thymus, mammary gland feminization, endometrial atrophy, localized focal necrosis of liver (visceral surface), atrophy of thymus cortex, decreased hematopoiesis in femoral/sternal bone marrow, mucosal ulcer of anterior stomach Reversibility: Hypertrophy of corpus luteum remained, but its frequency tended to decrease. Other findings were reversible.	<250	4.2.3.2.1
Male and female rats (Sprague Dawley)	i.v.	4-week treatment (QD)	0,[a] 0, 125, 250, 500	≥125: Increased serum amylase, small vesicular gland/prostate, decreased weight of ovary/uterus/submandibular gland, corpus luteum hypertrophy, endometrial hyperplasia, mucus degeneration of vaginal mucosal epithelium, mammary gland feminization/lobule hyperplasia, etc. ≥250: Decreases in red blood cell count/hemoglobin concentration/hematocrit, decreased white blood cell count, decreased eosinophil ratio, decreased hematopoiesis in femoral bone marrow, decreases in urinary sodium/chloride, localized interstitial edema at the renal papilla tip, degeneration of testicular spermatocytes, vesicular atrophy, hypertrophy of submandibular acinar cells, etc. 500: Soiled fur, emaciation, decreases in body weight/food consumption, decreases in serum ALT/urea nitrogen/total protein/α1 globulin/calcium, increases in serum glucose/cholesterol/phospholipids/chloride, decreased hematopoiesis in sternal bone marrow, enhanced extramedullary hematopoiesis in spleen, decreased urinary potassium, prostatic atrophy, decreased sperm count/cellular debris in epididymal lumen, regeneration of duodenal mucosal epithelium/neutrophil infiltration in lamina propria of the duodenum, etc.	<125	4.2.3.2.2
Male and female dogs (beagle)	i.v.	2-week treatment (QD) + 2-week withdrawal	0,[a] 0, 250, 500, 1,000	≥250: Reduced body weight gain, miosis ≥500: Relaxation of nictating membrane (transient) 1,000: Corneal opacity, light reflex lost Reversibility: Corneal opacity persisted, but its severity tended to decrease. Other findings were reversible.	<250	4.2.3.2.3
Male and female dogs (beagle)	i.v.	4-week treatment (QD)	0,[a] 0, 125, 250, 500	≥125: Loose feces, decreased uterine weight ≥250: Urinary ketone body positive 500: Light reflex lost, miosis, somnolence, tremor, increased serum phospholipid/triglycerides, increased liver weight, uterine atrophy	Male: 125 Female: <125	4.2.3.2.4

a) Only physiological saline was administered.

5.3 Genotoxicity

Genotoxicity studies on borofalan included a bacterial reverse mutation assay and a chromosomal aberration assay in mammalian cells (*in vitro* studies) and a rodent micronucleus assay (*in vivo* study). The studies showed borofalan to be non-genotoxic (Table 7). A rodent micronucleus assay was conducted on borofalan/BNCT. Results showed borofalan/BNCT to be genotoxic (Table 7).

From these studies, it was concluded that borofalan was non-genotoxic and borofalan/BNCT may induce micronuclei. Although no reverse mutation study was conducted on borofalan/BNCT, it was concluded that borofalan/BNCT may induce reverse mutation, based on reports that gene mutation is induced if cells containing ^{10}B at a certain concentration are irradiated with neutron beams (*Appl Radiat Isot*. 2009;67:S325-7, *Int J Radiat Oncol Biol Phys*. 2007;68:508-14, etc.).

Table 7. Genotoxicity studies (borofalan and borofalan/BNCT)

Study			Test system	Metabolic activation (treatment duration)	Concentration[a] or dose[b]	Result	Attached document CTD
Borofalan	*In vitro*	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA*	S9-/+	0, 313, 625, 1,250, 2,500, 5,000	Negative	4.2.3.3.1-1
		Chromosomal aberration assay in mammalian cells	Chinese hamster lung-derived fibroblasts	S9-/+ (6 hours)	0, 1,250,[e] 2,500,[e] 5,000[e]	Negative	4.2.3.3.1-2
				S9- (24 hours)	0, 1,250,[e] 2,500,[e] 5,000[e]	Negative	
	In vivo	Rodent micronucleus assay[c]	Male rats (Sprague Dawley) Peripheral blood		0, 125, 250, 500	Negative	4.2.3.2.2
Borofalan/ BNCT	*In vivo*	Rodent micronucleus assay[d]	Male mice (BALB/c) Bone marrow		0, 500, 1,000	Positive (>500)[f]	4.2.3.1.7

a) µg/plate or µg/mL
b) mg/kg/day
c) Borofalan was administered intravenously for 4 weeks.
d) Animals were given a single intravenous dose of borofalan and then irradiated with neutron beams for 30 or 40 minutes.
e) Precipitates were observed.
f) Immature erythrocytes containing micronuclei tended to increase also in the vehicle group irradiated with neutron beams for 40 minutes.

5.4 Carcinogenicity

Since borofalan is an antineoplastic agent intended for the treatment of patients with advanced cancer, no carcinogenicity study was conducted. The applicant explained that carcinogenicity of borofalan/BNCT cannot be excluded, given its possible genotoxicity [see Section 5.3].

5.5 Reproductive and developmental toxicity

Since borofalan is an antineoplastic agent intended for the treatment of patients with advanced cancer, no study was conducted on fertility and early embryonic development to implantation.

The applicant's explanation:

The possibility cannot be excluded that borofalan/BNCT may adversely affect the male and female fertility and early embryonic development, judging from the following observations:

- Borofalan/BNCT may be genotoxic [see Section 5.3].

- A repeated-dose toxicity study of borofalan in rats showed changes in mammary gland (feminization of male mammary gland and lobular hyperplasia of female mammary gland), male reproductive organs (degeneration of spermatocytes, decreased sperm count and cell debris in epididymal lumen, and atrophy of seminal vesicle and prostate gland), and ovary (corpus luteum hypertrophy), at exposure levels lower than the clinical exposure[9)] [see Section 5.2].

- Single-dose toxicity studies of borofalan in rats and dogs showed that serum or plasma prolactin concentration increased at exposure levels lower than the clinical exposure[9)] [see Section 5.7.1].

A study on the effect of borofalan on embryo-fetal and postnatal development was conducted in rats. At ≥500 mg/kg/day, the doses showing maternal toxicity, changes suggestive of growth inhibition such as low fetal weight and delayed ossification were observed, whereas no changes suggestive of teratogenicity were observed (Table 8).

The applicant' explanation:
Borofalan/BNCT may adversely affect embryo-fetal development, judging from the following findings:

- Decreased body weight, congenital anomaly, and delayed development were observed in neonates born to mothers that had received a high dose of boron orally (*Toxicological Profile for Boron*. U.S. Department of Health and Human Services. Public Health Service, Atlanta, Georgia;2010).

- Borofalan/BNCT may be genotoxic [see Section 5.3].

- Borofalan/BNCT was shown to be toxic in tissues that are thought to be highly sensitive to radiation according to Bergonie-Tribondeau's law (tongue, mucosal epithelia of digestive tract, hematopoietic cells in the bone marrow, and gonad gland) [see Section 5.1]. These results suggest that borofalan/BNCT may adversely affect embryo-fetal development as with X ray, γ-ray, etc., used in the radiotherapy of cancer.

Table 8. Reproductive toxicity (borofalan)

Study	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Study on embryo-fetal development and postnatal development	Female rats (Sprague Dawley)	i.v.	Gestation Days 7 to 17 (QD)	0, 500, 1,000	Maternal animals: <u>During gestation</u> ≥500: Decreases in body weight and food consumption 1,000: Decreased activity <u>Postpartum</u> Changes observed during gestation resolved. Fetuses: ≥500: Decreases in body weight and placental weight, delayed ossification 1,000: Increased rate of thymic cord Infants: 1,000: Decreased body weight (only on 4 days after birth) Tendency of decreased rate of pinna unfolding[a)]	General toxicity in maternal animals: <500 Fertility in maternal animals: 1,000 Fetuses: <500 Infants: 500	4.2.3.5.2

a) Pinna unfolding was observed in all animals on Day 4 after birth. This finding was therefore not considered to be toxicologically significant.

5.6 Local tolerance

Vasostimulation and skin primary irritation by borofalan were investigated in rabbits (Table 9). Borofalan was considered to be mildly irritating to blood vessels and surrounding tissues.

Table 9. Local tolerance study (borofalan)

Test system	Site of application	Testing method	Main findings	Attached document CTD
Male rabbits (NZW)	Blood vessel	0.05 mL of borofalan solution (0,[a)] 0, 30 mg/mL) was administered into posterior auricular vein that had been occluded by clipping both sides and, 3 minutes later, the vein was reperfused. The administration was repeated for 8 days, and the extent of thrombus formation and inflammatory reactions (hyperemia, swelling, and heat sensation, etc.) was evaluated before each administration and on the next day of the final dose.	Inflammation localized to the administration site was observed, but the extent of the borofalan-induced irritation was similar to that observed with physiological saline.	4.2.3.6.1
Male rabbits (NZW)	Skin	Borofalan (0.5 g) was applied to a lint lightly moisturized with water for injection, which was then placed on the skin (2.5 × 2.5 cm) and kept for 4 hours under occluded conditions. The primary skin irritation was evaluated after 1, 24, 48, and 72 hours according to Draize test.	None	4.2.3.6.2 (reference)

a) Only physiological saline was administered.

5.7 Other toxicity studies

5.7.1 Mechanism of toxicity

Histopathological changes were observed in the mammary gland and reproductive organs of male and female animals in the repeated-dose toxicity study in rats [see Section 5.2]. In order to elucidate the mechanism of these changes, concentrations of sex hormones (rats and dogs) and tyrosine (dogs) were measured (Table 10). An increase in serum or plasma prolactin concentration was observed in rats given borofalan ≥250 mg/kg. An increase in plasma prolactin concentration and a tendency of increase in serum tyrosine concentration were observed in dogs given borofalan ≥250 mg/kg.

Table 10. Studies on the mechanism of toxicity (borofalan)

Test system	Testing method	Main findings	Attached document CTD
Male and female rats (Sprague Dawley)	Borofalan (0, 0,[a] 250, 500, 1,000 mg/kg) was administered intravenously for 2 weeks to rats and, after a withdrawal period of 2 weeks [see Section 5.2], sex hormone concentrations in serum were measured.	≥250: Serum prolactin increased (males) ≥500: Serum testosterone tended to decrease (males). 1,000: Serum progesterone tended to increase (females) Reversibility: Yes	4.2.3.7.3.1 (reference)
Male and female rats (Sprague Dawley)	A single dose of borofalan (0, 500, 1,000 mg/kg) was administered intravenously to rats, and sex hormone concentrations in plasma were measured on 1, 3, and 7 days after administration.	≥500: Plasma prolactin increased (males and females). 1,000: Plasma progesterone increased (females)	4.2.3.1.2 4.2.3.7.3.2 (reference)
Male and female dogs (beagle)	A single dose of borofalan (0, 250, 500, 1,000 mg/kg) was administered intravenously to dogs, and sex hormone concentrations in plasma and tyrosine concentration in serum were measured at 1, 2, 4, 8, 24, and 72 hours after administration.	≥250: Plasma prolactin increased (males and females), serum tyrosine increased (females)	4.2.3.1.4 4.2.3.7.3.3 (reference)

a) Only physiological saline was administered.

5.7.2 Toxicity of impurities

Safety evaluation was conducted on impurities requiring qualification (L-tyrosine, L-phenylalanine, and N-acetyl-4-borono-L-phenylalanine) according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3A and Q3B Guidelines. It was determined that L-tyrosine and L-phenylalanine at the amount contained in the drug substance or in the drug product do not pose any safety problem, based on the following findings:

(a) The estimated exposure to L-tyrosine and L-phenylalanine (150 and 600 mg/day, respectively) following the administration of borofalan does not exceed the maximum daily doses in an infusion fluid containing vitamin B1, glucose, electrolyte, and amino acid (approximately 375 and 5,250 mg/day, respectively) (see package insert of Bfluid Injection 500 mL Bag, Bfluid Injection 1,000 mL Bag).

(b) L-tyrosine and L-phenylalanine are not genotoxic (*The EFSA Journal*. 2008;870:1-46, *Environmental Mutagen Research*. 2000;22:27-44).

Also, N-acetyl-4-borono-L-phenylalanine was determined to pose no safety problem at the amount contained in the drug substance or the drug product, based on the following findings:

(a) The bacterial reverse mutation assay was negative (Table 11),

(b) Findings observed in the 2-week repeated intravenous toxicity study of N-acetyl-4-borono-L-phenylalanine in rats were also observed in the 2-week repeated-dose toxicity study of borofalan, and the toxicity was minor (Table 12).

Table 11. Genotoxicity study (N-acetyl-4-borono-L-phenylalanine)

Study		Test system	Metabolic activation	Concentration (μg/plate)	Result	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA*	S9-/+	0, 313, 625, 1,250, 2,500, 5,000	Negative	4.2.3.7.6-2

Table 12. Repeated-dose toxicity study (N-acetyl-4-borono-L-phenylalanine)

Test system	Rout of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	i.v.	2 weeks (QD)	0, 31.5, 62.5, 125	≥31.5: Corpus luteum hypertrophy, mucus degeneration of vaginal mucosal epithelium, mammary gland lobule hyperplasia 125: Corpus luteum cyst, endometrial hyperplasia	Male: 125 Female: <31.5	4.2.3.7.6.1

5.7.3 Exposure dose in region outside neutron beam irradiation field

Following the administration of borofalan/BNCT, exposure dose in the region outside the neutron beam irradiation field in clinical settings was evaluated. The exposure dose was less than the skin tolerance dose in fractionated X-ray irradiation in humans (55-60 Gy; Guidelines for Treatment Planning of Radiation Therapy, 2016 edition) (Table 13). Taking account of the above results and of the report that single-dose irradiation at approximately ≥2 Gy causes skin disorder in humans (*The Japanese Journal of Nuclear Medicine*. 2003;40:213-20), the applicant explained that borofalan/BNCT therapy in humans has a low risk of causing skin disorder in the region outside irradiation field or, if any, would cause only mild skin disorder.

Table 13. Study on the exposure dose in region outside neutron beam irradiation field

Study type	Test system	Testing method	Main findings	Attached document CTD
In vitro	CHO cells	CHO cells were exposed to borofalan for 1 hour in the medium containing 25 ppm[a)] of borofalan, and the cell suspension was attached to a human model at the neck, chest, belly, groin, knee, and ankle. After neutron beam irradiation,[b)] the cells were recovered and the leakage dose (x-ray equivalent dose) was estimated from the number of micronuclei per 1,000 bi-nucleated cells.	Micronucleus count: 41.0 (non-irradiated), 216.5 (neck), 117.0 (chest), 99.5 (belly), 128.5 (groin), 114.0 (knee), 79.5 (ankle) Leakage dose expressed in terms of X-ray dose inducing the equivalent effect (Gy-Eq.): 1.57 (neck), 0.68 (chest), 0.52 (belly), 0.78 (groin), 0.65 (knee), 0.35 (ankle)	4.2.3.7.7

a) Boron concentration
b) The human model was irradiated for approximately 44 minutes at a dose of 12 Gy-Eq., using the radiation system design under the assumption that malignant brain tumor is present in the right temporal lobe.

5.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following sections, PMDA concluded that the applicant's explanations on the toxicity of borofalan are acceptable.

5.R.1 Toxicity of borofalan

The applicant explained the safety in humans regarding the following toxicities observed in the single and repeated dose toxicity studies in rats and dogs: (a) corneal opacity, (b) light reflex lost, miosis, somnolence, tremor, and relaxation of nictating membrane, (c) changes in mammary gland and male/female reproductive organs, (d) changes in kidney (including abnormal test values), and (e) changes in submandibular gland.

The applicant's explanation:

Following an intraperitoneal administration of ^{10}B-labeled 4-borono-L-phenylalanine to BALB/c mice, a transient decrease was observed in the activity of tyrosine oxidase, the enzyme responsible for metabolizing tyrosine to levodopa (*Cancer Res.* 1995;55:874-7). Also, prolactin and tyrosine levels increased in rats and dogs receiving borofalan [see Section 5.7.1]. These findings suggest the possibility that toxicity (a) was caused by increased level of tyrosine, toxicities (b) by decreased level of dopamine, and toxicities (c) by increased level of prolactin associated with decreased dopamine level. Although the mechanisms of the onset of toxicities (d) and (e) are unclear, toxicities (d) may be associated with the following observations.

(1) Borofalan is distributed in the kidney at a high concentration for a certain time period after administration [see Section 4.2.1].
(2) Borofalan is excreted mainly in urine [see Section 4.4.1].

The toxicities (a) through (e) occurred at the exposure level equal to or below the clinical exposure.[9)] In view of this observation and the estimated mechanism of onset, they may occur in humans as well. However, serious adverse events are unlikely to occur in humans given the observed reversibility of the toxicities.

PMDA's view:

PMDA accepted the applicant's explanation from the toxicological point of view, regarding the toxicity observed in the single and repeated dose toxicity studies of borofalan in rats and dogs.

5.R.2 Toxicity of borofalan/BNCT

The applicant explained the changes in hematopoietic and immunological organs, degeneration and necrosis of lingual mucosal epithelium, changes in male and female reproductive organs, and cataract, observed in the single-dose toxicity study of borofalan/BNCT in mice:

The applicant's explanation:

The above toxicity findings were not observed in the study of single dose of borofalan alone, and all of them are known to be caused by exposure to radiation. In mice, toxicity findings were observed in regions other than those close to the neutron beam irradiation field (e.g., tongue, eyes) because neutron beam irradiation to body parts other than the head and neck could not be avoided due to the small

body size. In humans, in contrast, body parts other than the head and neck are outside the irradiation field, and the exposure dose in the clinical use of borofalan/BNCT is lower than that in mice [see Section 5.1]. These facts suggest that serious adverse events are unlikely to occur in humans.

PMDA's view:
PMDA accepted the applicant's explanation from the toxicological point of view, regarding the systemic toxicity observed in the single dose toxicity study of borofalan/BNCT in mice.

5.R.3 Borofalan/BNCT in pregnant women or women who may be pregnant

PMDA asked the applicant to explain the use of borofalan/BNCT in pregnant women or women who may be pregnant.

The applicant's response:
Use of borofalan/BNCT in pregnant women or women who may be pregnant may adversely affect fetuses, for the following reasons:

(a) Borofalan/BNCT may induce micronuclei and reverse mutation [see Section 5.3].
(b) The reproductive and developmental toxicity study in rats showed decreased body weight, delayed ossification, and increased incidence of thymic cord in fetuses; and decreased body weight in the offspring [see Section 5.5].

Therefore, use of borofalan/BNCT in pregnant women or women who may be pregnant is not recommended. However, because borofalan/BNCT therapy targets diseases with an extremely poor prognosis, use of borofalan in pregnant women or women who may be pregnant should be permitted if the expected therapeutic benefits outweigh the possible risks associated with treatment, provided that the physician and the patient are well aware of the potential risk of borofalan/BNCT to the fetus.

PMDA accepted the explanation of the applicant.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Borofalan in human plasma and urine, and metabolites[10)] in urine were measured by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 0.0100, 5.00, and 5.00 μg/mL, respectively. Quantitation of boron in human whole blood was performed by inductively coupled plasma atomic emission spectrometry. The lower limit of quantitation was 0.5 ppm.

6.2 Clinical pharmacology

PK of borofalan in patients with cancer was investigated following an administration of borofalan alone.

10) M7 (phenylpyruvate form) and M9 (hydroxyphenyllactate form)

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study 001 [March 2014 to [redacted]])

An open-label, uncontrolled study was conducted to investigate PK of borofalan in 9 patients (9 patients included in the PK analysis) with unresectable locally recurrent head and neck squamous cell carcinoma or with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma.

A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h, and borofalan concentration in plasma, boron concentration in whole blood, and concentrations of borofalan and metabolites in urine were investigated. Starting at 2 hours after the start of administration of borofalan, a single-dose neutron beam irradiation was given using NeuCure BNCT System (BNCT30) for a maximum of 60 minutes at 10 Gy-Eq. (low dose) or 12 Gy-Eq. (high dose) as mucosal dose in the oral cavity, pharynx, or larynx.

Table 14 shows PK parameters of borofalan and boron. Boron concentration (range) in whole blood reached >20 ppm[11)] (24.6-35.8 ppm) at 2 hours after the start of administration, and remained at this level (24.4-33.3 ppm) even at 3 hours after the start of administration.

In urine samples collected up to 72 hours after the start of administration, mainly the unchanged borofalan was detected together with metabolites M7 and M9 (accounting for 50.4%, 6.49%, and 4.66%, respectively, of the administered dose). Renal clearance up to 72 hours after the start of administration was 2.38 L/h. The applicant explained that, in light of the renal clearance observed, CL/F of borofalan, and the results of the *in vitro* study using liver S9 fraction [see Section 4.3.1], borofalan is considered to be eliminated mainly by excretion from the kidney.

Table 14. PK parameters of borofalan and boron

Analyte	n	C_{max} (mg/mL[*1])	t_{max}[*2] (h)	AUC_{inf} (mg·h/mL[*3])	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Borofalan	9	0.812 ± 0.116	1.93 (1.92, 2.95)	5.81 ± 0.770	9.47 ± 1.16	4.72 ± 1.39	65.3 ± 23.1
Boron	9	28.6 ± 3.73	1.97 (1.92, 2.95)	328 ± 26.7	10.9 ± 1.75	3.98 ± 1.13	62.5 ± 20.9

Mean ± standard deviation; *1 ppm for boron; *2 Median (range); *3 ppm·h for boron

6.2.2 Administration of borofalan in patients with hepatic impairment

The applicant's explanation:

Results of the *in vitro* study with liver S9 fraction [see Section 4.3.1] suggest that borofalan is not metabolized in the liver. Therefore, it is unnecessary to adjust the dose of borofalan in patients with hepatic impairment.

11) Boron concentration of 20 ppm in whole blood was considered to be necessary for BNCT to be effective, for the following reasons: (1) In BNCT, it is essential that boron concentration in tumor exceeds 20 ppm and that boron concentration in tumor is kept at 20 ppm during neutron beam irradiation (*Clin Cancer Res*. 2005;11:3987-4002), and (2) in the tissue distribution study in nude mice subcutaneously transplanted with human glioblastoma-derived U-87MG cell line, radioactivity concentration was higher in tumor than in whole blood [see Section 4.2.1].

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the applicant's explanations on the clinical pharmacology of borofalan are acceptable except for those described in the following sections.

6.R.1 Administration of borofalan in patients with renal impairment

The applicant's explanation about administration of borofalan in patients with renal impairment:

Borofalan is eliminated mainly by excretion from kidney [see Section 6.2.1.1], which suggests that caution is necessary in administering borofalan to patients with renal impairment. However, currently available information described below suggests that there is little need to adjust the dose of borofalan in these patients, although there is limited experience of administration of borofalan in this patient group in the Japanese phase I study (Study 001) and the Japanese phase II study (Study 002).

- In Studies 001 and 002, the incidence of all adverse events in patients with normal renal function[12)] (n = 22), patients with mild renal impairment (n = 5), patients with moderate renal impairment (n = 3) was 100% in all groups, and the incidence of Grade ≥3 adverse events was 68%, 60%, and 100%, respectively, showing no clear relationship between the severity of renal impairment and the incidence of adverse events.

- Most of the adverse events observed only in patients with moderate renal impairment occurred in a single patient who discontinued the study because of aggravation of the primary disease; this suggests that the adverse events in this patient may have been caused by the aggravation of the primary disease.

PMDA's view:

PMDA generally accepted the explanation of the applicant. However, since information on PK of borofalan in patients with renal impairment is important for the proper use of borofalan, the relevant information should be collected continuously, and new information should be provided appropriately to healthcare professionals when it becomes available.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from 2 studies: 1 Japanese phase I study and 1 Japanese phase II study (Table 15).

[12)] (a) Normal renal function: Estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCL; mL/min/1.73 m^2) is above the lower limit of reference range and protein urine is <2+ or urinary protein/creatinine ratio is ≤0.5.
(b) Mild renal impairment: eGFR or CrCL (mL/min/1.73 m^2) is ≥60 and below the lower limit of reference range and protein urine is 2+ or urinary protein/creatinine ratio is >0.5.
(c) Moderate renal impairment: eGFR or CrCL (mL/min/1.73 m^2) is ≥30 and ≤59.
(d) Severe renal impairment: eGFR or CrCL (mL/min/1.73 m^2) is <30.
No patients with severe renal impairment were enrolled in the Japanese phase I study (Study 001) or in the Japanese phase II study (Study 002).

Table 15. List of clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Study population	No. of enrolled subjects	Outline of dosage regimen	Major endpoints
Evaluation	Japan	001	I	Patients with unresectable locally recurrent head and neck squamous cell carcinoma or with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma	9 (a) 6 (b) 3	(a) A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h. A single-dose neutron beam irradiation (10 Gy-Eq.)[*1] was started at 2 hours after the start of administration of borofalan.[*2] (b) A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h. A single-dose neutron beam irradiation (12 Gy-Eq.)[*1] was started at 2 hours after the start of administration of borofalan.[*2]	Safety Tolerability
		002	II	(a) Patients with post-CRT or -RT unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma	21	A single dose of borofalan was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during neutron beam irradiation. A single-dose neutron beam irradiation (12 Gy-Eq.)[*1] was started at 2 hours after the start of administration of borofalan.[*2]	Efficacy Safety

[*1] Dose given to mucosa of the oral cavity, pharynx, or larynx; [*2] BNCT30 was used.

The outline of each clinical study is shown below. Main adverse events other than death observed in each clinical study are described in Section "7.2 Adverse events, etc. observed in clinical studies," and study results on PK in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase I study (CTD 5.3.3.2-1 and 5.3.3.2-2, Study 001 [March 2014 to [redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and tolerability of borofalan/BNCT in patients with unresectable locally recurrent head and neck squamous cell carcinoma or patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma[13)] (target sample size, 12 subjects at the maximum) in 2 study sites in Japan.

A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h. Starting at 2 hours after the start of administration of borofalan, a single-dose neutron beam irradiation was given using BNCT30 for a maximum of 60 minutes at 10 Gy-Eq. (low dose) or 12 Gy-Eq. (high dose) as mucosal dose in the oral cavity, pharynx, or larynx.

13) The study enrolled patients who met both of the following criteria:
(a) Head and neck squamous cell carcinoma with prior RT at ≥40 and ≤75 Gy to the target lesion, or head and neck non-squamous cell carcinoma with prior RT at ≤75 Gy to the target lesion.
(b) The last irradiation to the target lesion was performed 180 or more days before the enrollment.

All of the 9 patients enrolled in the study (6 in the low dose group, 3 in the high dose group) received borofalan/BNCT, and were included in the safety analysis population.

The dose-limiting toxicity (DLT)[14] evaluation period was up to Day 90 after administration of borofalan/BNCT. DLT (Grade 3 dysphagia) was observed in 1 of 6 patients in the low dose group, whereas no DLT was observed in the high dose group. Therefore, the recommended dose of borofalan/BNCT was determined to be 12 Gy-Eq.

No death occurred during treatment with borofalan/BNCT or during 90 days after the treatment.

7.1.1.2 Japanese phase II study (CTD 5.3.5.2-1, Study 002 [June 2016 to [redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of borofalan/BNCT in (a) patients with post-CRT or -RT unresectable locally recurrent[15] head and neck squamous cell carcinoma[16] and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma[17] (target sample size, 21 subjects) in 2 study sites in Japan.

A single dose of borofalan was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, and at 100 mg/kg/h during the neutron beam irradiation. Starting at 2 hours after the start of administration of borofalan, a single-dose neutron beam irradiation was given using BNCT30 for a maximum of 60 minutes at 12 Gy-Eq. as mucosal dose in the oral cavity, pharynx, or larynx.

All of the 21 patients enrolled in the study received borofalan/BNCT, and were included in the efficacy analysis population and the safety analysis population.

The primary endpoint of the study was response rate assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1.

Table 16 shows the results of response rate assessed by BICR based on RECIST ver.1.1, the primary efficacy endpoint of the study. The lower limit of 90% confidence interval (CI) of the response rate exceeded the prespecified threshold response rate (20.0%).[18]

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14) DLT was defined as Grade ≥3 nonhematological toxicity and Grade ≥4 hematological toxicity for which a causal relationship to BNCT could not be ruled out. Among these events, those meeting both of the following criteria were not considered as DLT: (i) Adverse events common to existing RT ([a] Grade 3 mucositis oral, pharyngeal mucosa inflammation, laryngeal mucosa inflammation, dry mouth, and salivary gland inflammation; [b] Grade ≥3 fatigue, anorexia, headache, ear pain. vertigo, nausea, vomiting, and serum amylase increased (salivary gland type), and [c] Grade ≥4 anaemia, white blood cell decreased, platelets decreased, lymphopenia, and neutropenia), and (ii) serious adverse events that resolved without surgical intervention.

15) The study also enrolled patients who showed partial response (PR) or stable disease (SD) after CRT or RT but required additional treatment for residual tumor.

16) The following patients were enrolled: (a) Patients who received [i] platinum-based CRT or [ii] platinum-based induction chemotherapy + RT. (b) Patients showing local recurrence within 6 months after completing [i] RT alone, [ii] non-platinum-based CRT, or [iii] CRT including cetuximab who were intolerant to, or refused, platinum-based chemotherapy. The study also enrolled patients who showed local recurrence at >6 months after completing multimodality therapy including RT if they had disease progression or recurrence during or after platinum-based chemotherapy or if they were intolerant to, or refused, platinum-based chemotherapy.

17) These patients were enrolled regardless of prior RT or chemotherapy.

18) The threshold response rate was set at 20% based on the clinical data in patients receiving 5-FU and a platinum antineoplastic drug in a foreign phase III study (Study EMR62202-002 [EXTREME study]), which was conducted to compare the efficacy and safety of cetuximab/5-FU/platinum antineoplastic drug and 5-FU/platinum antineoplastic drug in patients with recurrent or metastatic head and neck squamous cell carcinoma without a prior chemotherapy (*N Engl J Med*. 2008;359:1116-27).

Table 16. Best overall response and response rate
(RECIST ver.1.1, efficacy analysis population, BICR assessment, data cut-off [redacted])

Best overall response	n (%) N = 21
CR	5 (23.8)
PR	10 (47.6)
SD	5 (23.8)
PD	0
NE	1 (4.8)
Response (CR+PR) (response rate [90% CI*] (%))	15 (71.4 [51.3, 86.8])

* Clopper-Pearson method

No death occurred during, or within 90 days after, treatment with borofalan/BNCT.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA concluded that, among the evaluation data submitted, the most important clinical study for evaluating the efficacy and safety of borofalan/BNCT was the Japanese phase II study (Study 002) conducted to investigate the efficacy and safety of borofalan/BNCT in (a) patients with post-CRT or -RT unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma. PMDA therefore decided to evaluate the submitted data focusing on Study 002.

7.R.2 Clinical positioning and efficacy

On the basis of the following review, PMDA has concluded that a certain level of efficacy of borofalan/BNCT has been demonstrated in patients with unresectable, locally advanced or locally recurrent head and neck cancer.

7.R.2.1 Clinical positioning

The description on borofalan/BNCT was not found in Japanese or foreign clinical practice guidelines or representative textbooks on clinical oncology.

The applicant's explanation about the treatment algorithm for patients with unresectable, locally advanced or locally recurrent head and neck cancer and about the clinical positioning of borofalan/BNCT in the treatment algorithm:
Among patients with unresectable, locally advanced or locally recurrent head and neck cancer, those with squamous cell carcinoma are treated, as the standard treatment, (i) with nivolumab if local recurrence is observed within 6 months after CRT or RT and (ii) with cetuximab, nivolumab, etc., if local recurrence is observed at >6 months after CRT or RT.

In patients with non-squamous cell carcinoma, which accounts for only approximately 10% of head and neck cancer, it is practically impossible to obtain evidence for establishing the standard treatment. For this reason, these patients are treated in a similar manner as in patients with squamous cell carcinoma in clinical practice (*Shin Rinsho Shuyo Gaku*, 5th revised edition [Nankodo, 2018]).

Patients with head and neck cancer may experience dysfunctions in vocalization, swallowing, mastication, respiration, etc. because of locally advanced or locally recurrent lesion. In Study

ONO-4538-11/CA209141 (CheckMate 141 study),[19] the response rate [95% CI] assessed by the investigator based on RECIST ver.1.1 was 13.3% [9.3%, 18.3%] (*N Engl J Med*. 2016;375:1856-67); this suggests that nivolumab has only a limited therapeutic effect on head and neck cancer. In addition, re-irradiation after CRT or RT is not established as a standard treatment because it may exceed the tolerance dose in the normal tissues around the tumor, posing an increased risk of serious adverse drug reactions (*Int J Radiat Oncol Biol Phys*. 2011;81:1211-9).

In contrast, borofalan/BNCT is a local treatment in which ^{10}B, a nuclide species highly reactive with neutron, is incorporated into tumor cells which are then disrupted by the reaction between ^{10}B atoms and neutrons. This treatment has little effect on normal cells surrounding the tumor and is expected to preserve functions such as vocalization, swallowing, mastication, and respiration by controlling local lesions. The treatment is therefore considered to be positioned as one of the local treatments for patients with unresectable, locally advanced or locally recurrent head and neck cancer.

PMDA accepted the explanation of the applicant.

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about efficacy endpoints and evaluation results of Study 002:
Patients with unresectable, locally advanced or locally recurrent head and neck cancer who respond to treatment with borofalan/BNCT can preserve the functions of vocalization, swallowing, mastication, respiration etc. The treatment is thus expected to increase QOL of patients, which is of clinical significance. Therefore, the response rate was selected as the primary endpoint in Study 002.

In Study 002, the response rate [90% CI] was 71.4% [51.3%, 86.8%], with the lower limit exceeding the prespecified threshold response rate [see Section 7.1.1.2]. Table 17 shows the results classified by tissue type ([a] squamous cell carcinoma, [b] non-squamous cell carcinoma). No clear difference was observed in the response rate between these tissue types. Based on the above, borofalan/BNCT is expected to be effective in the patient population in Study 002, regardless of tissue type ([a] squamous cell carcinoma, [b] non-squamous cell carcinoma).

Table 17. Best overall response and response rate by tissue type ([a] squamous cell carcinoma, [b] non-squamous cell carcinoma) (RECIST ver.1.1, efficacy analysis population, BICR assessment, data cut-off [redacted])

Best overall response	n (%)	
	(a) Patients with squamous cell carcinoma (N = 8)	(b) Patients with non-squamous cell carcinoma (N = 13)
CR	4 (50.0)	1 (7.7)
PR	2 (25.0)	8 (61.5)
SD	1 (12.5)	4 (30.8)
PD	0	0
NE	1 (12.5)	0
Response (CR + PR) (response rate [90%CI*] (%))	6 (75.0 [40.0, 95.4])	9 (69.2 [42.7, 88.7])

* Clopper-Pearson method

[19] A global phase III study conducted to compare the efficacy and safety of nivolumab and an investigator-selected drug (cetuximab, methotrexate, or docetaxel hydrate) in patients with recurrent or metastatic head and neck squamous cell carcinoma of oral, oropharyngeal, hypopharyngeal, or laryngeal origin who showed disease progression or recurrence within 6 months after the completion of platinum-based chemotherapy (including radical or postoperative chemoradiotherapy).

PMDA's view:

Since Study 002 was an open label, uncontrolled study without long-term data, there are limitations to evaluating, based on the results of the study, the efficacy of borofalan/BNCT in patients with unresectable, locally advanced or locally recurrent head and neck cancer. However, taking account of the review in Section "7.R.2.1 Clinical positioning" and of the following points, PMDA considers that borofalan/BNCT has showed a certain level of efficacy in these patients:

- Localized lesions in patients with unresectable, locally advanced or locally recurrent head and neck cancer may severely impair QOL of patients by causing dysphagia, malnutrition, airway stenosis, aspiration, fistulization, etc. Localized control of the lesions is considered to have a certain level of clinical significance.

- In Study 002, patients showed a certain level of response to borofalan/BNCT.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events, etc. observed in clinical studies"]

Based on the review described in the sections below, PMDA considers that particular attention should be paid to the following adverse events when administering borofalan/BNCT to patients with unresectable, locally advanced or locally recurrent head and neck cancer: dysphagia, brain abscess, skin disorder, crystal urine, cataract, and carotid haemorrhage.

Attention should be paid to the above adverse events in using borofalan/BNCT. However, PMDA has concluded that borofalan/BNCT is tolerable provided that appropriate actions, such as monitoring and controlling of adverse events, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of borofalan/BNCT, based on the safety information obtained from Studies 002 and 001:

Table 18 shows the outline of safety in Studies 002 and 001.

Table 18. Outline of safety (Studies 002 and 001)

	n (%)	
	Study 002	Study 001
	N = 21	N = 9
All adverse events	21 (100)	9 (100)
Grade ≥3 adverse events	18 (85.7)	3 (33.3)
Adverse events leading to death	0	0
Serious adverse events	1 (4.8)	1 (11.1)
Adverse events leading to discontinuation of borofalan/BNCT	0	0

In Study 002, all-grade adverse events with an incidence of ≥20% were alopecia in 19 patients (90.5%), amylase increased in 18 patients (85.7%), nausea in 17 patients (81.0%), dysgeusia in 15 patients (71.4%), parotitis and decreased appetite in 14 patients (66.7%) each, stomatitis in 13 patients (61.9%), vomiting in 10 patients (47.6%), malaise, thirst, and radiation skin injury in 9 patients (42.9%) each, conjunctivitis and sialoadenitis in 7 patients (33.3%) each, blood prolactin abnormal and blood prolactin increased in 6 patients (28.6%) each, and constipation in 5 patients (23.8%). Grade

≥3 adverse events were amylase increased in 16 patients (76.2%), lymphopenia, lymphocyte count decreased, stomatitis, brain abscess,[20)] and radiation skin injury in 1 patient (4.8%) each. Brain abscess[20)] in 1 patient (incidence 4.8%) was the only serious adverse event observed, and its causal relationship to borofalan/BNCT could not be ruled out. No adverse events led to death or discontinuation of borofalan/BNCT.

In Study 001, all-grade adverse events reported by ≥3 patients were haematuria in 9 patients (100%), malaise and alopecia in 8 patients (88.9%) each, blood prolactin abnormal in 7 patients (77.8%), face oedema, amylase increased, C-reactive protein increased, hypoalbuminaemia, and decreased appetite in 6 patients (66.7%) each, nausea, stomatitis, and lymphopenia in 5 patients (55.6%) each, conjunctivitis, hyperglycaemia, proteinuria, laryngeal inflammation, and hypertension in 4 patients (44.4%) each, anaemia, lacrimation increased, constipation, application site erythema, influenza like illness, pain, pyrexia, radiation skin injury, hypertriglyceridaemia, hyponatraemia, headache, urine abnormality, and pharyngeal inflammation in 3 patients (33.3%) each. Grade ≥3 adverse events were lymphocyte count decreased in 3 patients (33.3%), anaemia, dysphagia,[21)] upper gastrointestinal haemorrhage, hypercalcaemia, hypoalbuminaemia, pharyngeal haemorrhage, pharyngeal inflammation, laryngeal inflammation, and hypertension in 1 patient (11.1%) each. Dysphagia[21)] in 1 patient (incidence 11.1%) was the only serious adverse event observed, and its causal relationship to borofalan/BNCT could not be ruled out. No adverse events led to death or discontinuation of borofalan/BNCT.

PMDA asked the applicant to explain the mechanism of increase in amylase by borofalan/BNCT and actions that should be taken in response to this event.

The applicant's response:
(a) Both in Studies 002 and 001, the observed increase in amylase was due to an increase in salivary gland-type amylase, and (b) salivary gland injury with radiation leads to an increase in salivary gland-type amylase (*Strahlenther Onkol*. 1990;166:688-95); this suggests that the observed increase in amylase was due to borofalan/BNCT. However, an increase in amylase is considered to be well tolerated because, in both studies, (a) the increase in salivary gland-type amylase was transient, and no objective findings associated with the increase in amylase were observed, and (b) the increased amylase resolved during follow-up without any additional treatment.

PMDA's view:
In treatment with borofalan/BNCT, attention should be paid to the serious adverse events and Grade ≥3 adverse events that occurred in Studies 002 and 001 as well as adverse events that occurred frequently in the studies. Information on the incidence of these events should be provided

[20)] A 50-year-old woman. On Day 54 after borofalan/BNCT, she had disturbances in consciousness and visited another hospital, where she was diagnosed with cerebral edema. On Day 55, external decompression was performed on the cerebral edema, which resulted in discharge of pus from inside the cranium. This confirmed that the disturbed consciousness had been caused by cerebral abscess. Cerebral abscess drainage was performed and treatment with antibiotics was started. On Day 265, findings associated with cerebral abscess disappeared, and cerebral abscess was considered as "resolved."

[21)] A 68-year-old woman. From 26 days before the enrollment in the study, she had dysphagia (Grade 2) as a concurrent illness. On Day 6 after borofalan/BNCT, dysphagia worsened (Grade 3). Contrast CT on Day 32 showed a shrinkage of the irradiated lesion (left posterior oropharyngeal wall). However, dysphagia worsened due to a new lesion which developed from outside the irradiated area and, on Day 95, the patient died of disease progression.

appropriately to healthcare professionals. Because of the extremely limited safety information available on borofalan/BNCT in patients with head and neck cancer, relevant information should be collected continuously after the market launch and new information should be provided to healthcare professionals promptly when it becomes available.

In the following sections, PMDA reviewed the safety of borofalan/BNCT, based on the safety results in Studies 002 and 001, focusing on serious adverse events for which a causal relationship to borofalan/BNCT could not be ruled out and on Grade ≥3 adverse events occurring frequently in the studies.

7.R.3.2 Dysphagia

The applicant's explanation about dysphagia caused by borofalan/BNCT:

As for dysphagia, the applicant collected events[22)] classified as the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs): "endoscopic swallowing evaluation," "endoscopic swallowing evaluation abnormal," "swallow study," "swallow study abnormal," "odynophagia," "dysphagia," "dysphagia lusoria," "malignant dysphagia," "radiation dysphagia," "aerophagia," or "sideropenic dysphagia."

In Study 002, all-grade dysphagia was observed in 1 of 21 patients (4.8%; Grade 1 odynophagia). There were no cases of serious dysphagia, or dysphagia leading to death or discontinuation of borofalan/BNCT.

In Study 001, all-grade dysphagia was observed in 1 of 9 patients (11.1%; Grade-3 dysphagia). Serious dysphagia was observed in 1 of 9 patients (11.1%; dysphagia[21)]). Its causal relationship to borofalan/BNCT could not be ruled out. There were no cases of dysphagia leading to death or discontinuation of borofalan/BNCT.

The time to the first onset of dysphagia was 5 days in Study 002 and 7 days in Study 001.

PMDA's review:

Serious dysphagia for which a causal relationship to borofalan/BNCT could not be ruled out was observed in a submitted clinical study, warranting caution against dysphagia in treatment with borofalan/BNCT. Information on the incidences of dysphagia in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

7.R.3.3 Brain abscess

The applicant's explanation about brain abscess caused by borofalan/BNCT:

As for brain abscess, the applicant collected events[22)] classified as MedDRA PT "amoebic brain abscess" or "brain abscess." No brain abscess was observed in Study 001.

In Study 002, all-grade brain abscess was observed in 1 of 21 patients (4.8%; Grade 3 brain abscess). Serious brain abscess was observed in 1 of 21 patients (4.8%; brain abscess in 1 patient[20)]), and its

22) MedDRA ver. 19.0 was used in Study 002 and ver. 18.1 in Study 001.

causal relationship to borofalan/BNCT could not be ruled out. There were no cases of brain abscess leading to death or discontinuation of borofalan/BNCT.

PMDA's view:
Serious brain abscess for which a causal relationship to borofalan/BNCT could not be ruled out was observed in a submitted clinical study, warranting caution against brain abscess in treatment with borofalan/BNCT. Information on the incidences of brain abscess in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

7.R.3.4 Radiation skin injury

The applicant's explanation about radiation skin injury caused by borofalan/BNCT:
As for radiation skin injury, the applicant collected events[22)] classified as MedDRA PT "radiation skin injury" or "recall phenomenon."

In Study 002, all-grade radiation skin injury was observed in 9 of 21 patients (42.9%, radiation skin injury in 9 patients). Grade ≥3 radiation skin injury was observed in 1 of 21 patients (4.8%; radiation skin injury in 1 patient). There were no cases of serious radiation skin injury or radiation skin injury leading to death or discontinuation of borofalan/BNCT.

In Study 001, all-grade radiation skin injury was observed in 3 of 9 patients (33.3%; radiation skin injury in 3 patients). There were no cases of Grade ≥3 radiation skin injury, serious radiation skin injury, or radiation skin injury leading to death or discontinuation of borofalan/BNCT.

The median time (range) to the first onset of radiation skin injury was 8 days (2-30 days) in Study 002 and 3 days (2-8 days) in Study 001.

PMDA's view:
In the submitted clinical studies, skin disorder was observed at a certain incidence following administration of borofalan/BNCT. Also, skin disorder is a known risk of irradiation, warranting caution against skin disorder in treatment with borofalan/BNCT. Therefore, information on the incidence of skin disorder in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

7.R.3.5 Renal dysfunction

The applicant's explanation about renal dysfunction caused by borofalan/BNCT:
As for renal dysfunction, the applicant collected events classified as MedDRA system organ class (SOC) "renal and urinary disorders" or MedDRA high level group term (HLGT) "renal and urinary tract investigations and urinalyses."

Table 19 shows the incidence of renal dysfunction in Studies 002 and 001.

Table 19. Incidence of renal dysfunction (Studies 002 and 001)

PT*	n (%)			
	Study 002 (N = 21)		Study 001 (N = 9)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal dysfunction	2 (9.5)	0	9 (100)	0
Haematuria	2 (9.5)	0	9 (100)	0
Dysuria	2 (9.5)	0	0	0
Proteinuria	0	0	4 (44.4)	0
Urine abnormality	0	0	3 (33.3)	0
Crystal urine	0	0	2 (22.2)	0
Urinary tract pain	0	0	2 (22.2)	0
Cystitis noninfective	0	0	2 (22.2)	0
Urine output decreased	0	0	1 (11.1)	0
Neurogenic bladder	0	0	1 (11.1)	0

* The MedDRA version 19.0 was used in Study 002 and version 18.1 in Study 001.

In Studies 002 and 001, there were no cases of serious renal dysfunction or renal dysfunction leading to death or discontinuation of borofalan/BNCT.

The median time (range) to the first onset of renal dysfunction was 1 day (1-1 day) in Study 002 and 1 day (1-50 days) in Study 001.

PMDA asked the applicant to explain the mechanism of borofalan/BNCT-induced renal dysfunction and how to prevent it.

The applicant's response:
In toxicity studies, rats showed colored urine and dogs showed precipitates supposedly consisting of borofalan in urinary crystalline sediment [see Section 5.1]. These crystals are likely to induce renal dysfunction such as hematuria.

In Study 001, water intake before borofalan/BNCT was prohibited for the purpose of accurate PK measurement. In Study 002, in contrast, water intake after borofalan/BNCT was recommended as necessary in order to prevent renal dysfunction induced by borofalan crystals in urine. The percentage of patients who experienced renal dysfunction was lower in Study 002 than in Study 001, presumably as a result of water intake. These results suggest that renal dysfunction is preventable by drinking water after borofalan/BNCT, as appropriate.

PMDA's view:
In the submitted clinical studies, all events of borofalan/BNCT-induced renal dysfunction was Grade ≤2. However, attention should be paid to adverse events associated with urinary crystals in treatment with borofalan/BNCT, because (1) borofalan/BNCT caused renal dysfunction supposedly associated with urinary crystals, at a certain incidence, and (2) in Study 002, taking a preventive action against urinary crystals was recommended. Therefore, the package insert should state that urinary crystals may occur in patients treated with borofalan/BNCT, and healthcare professionals should be appropriately informed, via the package insert, about the preventive action recommended in Study 002.

7.R.3.6 Cataract

The applicant's explanation about borofalan/BNCT-induced cataract:

As for cataract, the applicant collected events[22)] classified as MedDRA PT "cataract" or "radiation cataract." Cataract was not observed in Study 001.

In Study 002, all-grade cataract was observed in 2 of 21 patients (9.5%; cataract in 2 patients). There were no cases of Grade ≥3 cataract, serious cataract, or cataract leading to death or discontinuation of borofalan/BNCT.

The median time (range) to the first onset of cataract in Study 002 was 67 days (34-100 days).

PMDA's view:
In a submitted clinical study, cataract was observed at a certain incidence following administration of borofalan/BNCT, and cataract is a known risk of radiation exposure. Therefore, attention should be paid to borofalan/BNCT-induced cataract. Information on the incidence of cataract in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

7.R.3.7 Safety in patients with tumor infiltration into carotid artery

The applicant's explanation about the safety in patients with tumor infiltration into carotid artery:
Bleeding from carotid artery occurred after borofalan/BNCT in patients who had tumor infiltration into carotid artery or to a wide area of skin after radiotherapy (*Appl Radiat Isot*. 2015;106:202-6). Therefore, the package insert will include a statement that borofalan/BNCT may cause carotid haemorrhage in patients with tumor infiltration into carotid artery, to raise cautions.

Since the carotid artery becomes fragile after radiotherapy, patients with circumferential tumor infiltration to the carotid artery are extremely likely to experience carotid haemorrhage after receiving borofalan/BNCT. Therefore, borofalan/BNCT will be contraindicated in this patient group.

PMDA's view:
PMDA generally accepted the applicant's explanation. Given the mechanism of action of borofalan/BNCT, carotid haemorrhage is likely to occur and, once it occurs, it may become serious. Therefore, attention should be paid to carotid haemorrhage. To raise cautions, healthcare professionals should be appropriately informed, via the package insert, that carotid haemorrhage may occur in patients treated with borofalan/BNCT.

7.R.3.8 Safety in patients within <90 days after receiving the last RT at the site of lesion

The applicant's explanation about the safety in patients within <90 days after receiving the last RT at the site of lesion:
Patients within <90 days after receiving the last RT at the site of lesion were excluded from Study 002 for the following reasons: (a) The efficacy evaluation of RT may have not been established, and (b) cumulative dose of RT may affect the safety of borofalan/BNCT. Thus, clinical safety data on borofalan/BNCT in this patient group are unavailable. However, because the cumulative dose in the normal tissue after RT cannot be accurately measured, whether to repeat radiotherapy is determined based on the clinical symptoms of organs in the radiation field as well as on the cumulative dose and

the tolerance dose of organs in the radiation field; this suggests that it is acceptable to administer borofalan/BNCT to (a) patients who did not respond to RT and (b) patients without Grade ≥3 adverse events in the radiation field.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, since no clinical study data are available on the efficacy and safety of borofalan/BNCT in patients who received the last RT on the lesion site less than 90 days before, healthcare professionals should be appropriately informed, via the package insert, that this patient group was excluded from Study 002.

7.R.3.9 Safety in patients who received radiotherapy in a total dose of ≥75 Gy at the lesion site

The applicant's explanation about the safety in patients who received radiotherapy in a total dose of ≥75 Gy at the lesion site:
Since radiotherapy in a total dose of ≥75 Gy at a lesion site exceeds the standard radiation dose, patients who had received such a treatment were excluded from Study 002. Therefore, no efficacy or safety data of borofalan/BNCT in this patient group are available. However, because whether to repeat radiotherapy is determined based on the cumulative dose, tolerance dose, and clinical symptoms of the organs within the radiation field, borofalan/BNCT in these patients is considered to be acceptable, although clinical symptoms of organs within the radiation field should be carefully monitored.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, since no clinical study data are available on the efficacy and safety of borofalan/BNCT in patients who had received radiotherapy in a total dose of ≥75 Gy at the lesion site, healthcare professionals should be appropriately informed, via the package insert, that this patient group was excluded from Study 002.

7.R.3.10 Safety in patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface

The applicant's explanation about the safety in patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface:
The incidence of mucositis in patients receiving RT for head and neck cancer was 80% and the incidence of Grade 3 or 4 mucositis was 39% (*Radiother Oncol*. 2003;66:253-62). In Study 001, the recommended radiation dose of borofalan/BNCT was 12 Gy-Eq., based on the tolerance dose of the mucous membrane [see Section 7.1.1.1]. Based on the above, in Study 002, patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface were excluded, in order to accurately evaluate the occurrence of adverse events in mucous membrane. As a result, efficacy and safety data of borofalan/BNCT in this patient group are unavailable. However, since the radiation dose applied to the mucous membrane of these patients will be less than 12 Gy-Eq., whether to administer borofalan/BNCT to these patients can be determined based on the cumulative dose and the tolerance dose in the normal tissue other than mucous membrane within the radiation field.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, since no clinical data are available on the efficacy and safety of borofalan/BNCT in patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface, healthcare professionals should be appropriately informed, via the package insert, that this patient group was excluded from Study 002.
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7.R.4 Indications

The proposed indications for borofalan/BNCT were "Unresectable locally recurrent head and neck cancer" and "Unresectable advanced head and neck non-squamous cell carcinoma." The Precautions Concerning Indication section included the following statement:

- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

In view of the reviews in Sections "7.R.2 Clinical positioning and efficacy" and "7.R.3 Safety" and the discussion described in the following sections, PMDA concluded that the indication should be "Unresectable, locally advanced or locally recurrent head and neck cancer" and that the Precautions Concerning Indication section should include the following precautionary statements:

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.
- The efficacy and safety of borofalan as adjuvant therapy have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

7.R.4.1 Target patients for borofalan/BNCT and indications

The applicant's explanation about target patients for borofalan/BNCT and indications:
On the basis of the results of Study 002 [see Sections 7.1.1.2 and 7.R.2], the applicant considers that borofalan/BNCT is positioned as a treatment option for patients with unresectable, locally advanced or locally recurrent head and neck cancer.

Study 002 did not include patients with unresectable locally advanced head and neck squamous cell carcinoma, and therefore clinical data of borofalan/BNCT in these patients have not been obtained. However, borofalan/BNCT is a treatment option for them as well because current treatment for them is similar to that for patients with unresectable locally recurrent head and neck squamous cell carcinoma.

Based on the above, the applicant has proposed the following indications for borofalan/BNCT: "Unresectable locally recurrent head and neck cancer" and "Unresectable advanced head and neck non-squamous cell carcinoma." Details of patients treated in Study 002 will be described in the Clinical Studies section of the package insert and the following precautionary statement will be included in the Precautions Concerning Indication section.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

In addition, clinical data of borofalan/BNCT have not been obtained from patients with metastatic head and neck cancer or patients with head and neck cancer eligible for adjuvant therapy after surgery. Borofalan/BNCT is not recommended for these patients.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, the efficacy of borofalan/BNCT was evaluated mainly based on the response rate in Study 002, and no information on the survival benefit is available. Therefore, patients eligible for the standard therapy (including local treatments such as CRT) should be treated with the standard therapy in preference to borofalan/BNCT; this should be communicated to physicians to urge caution.

Also, since clinical data on the efficacy and safety of borofalan/BNCT as an adjuvant therapy are unavailable, borofalan/BNCT is not recommended for patients requiring adjuvant therapy. This caution should be included in the Precautions Concerning Indication section.

On the basis of the above review, the indication should be "unresectable, locally advanced or locally recurrent head and neck cancer." Details of patients treated in Study 002 should be described in the "Clinical Studies" section of the package insert, and the following precautionary statements should be included in the Precautions Concerning Indication section:

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.
- The efficacy and safety of borofalan as adjuvant therapy have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

7.R.5 Dosage and administration

The proposed dosage regimen for borofalan was "Usually, for adults, a single dose of 500 mg/kg of borofalan (^{10}B) is administered as an intravenous infusion over 3 hours, at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during the last 1 hour. Irradiation of neutron beams to the cancer area is started at 2 hours after the start of intravenous infusion. The intravenous infusion is terminated at the end of irradiation. (In a patient weighing 60 kg, 800 mL of Steboronine solution is intravenously infused over 2 hours, followed by intravenous infusion of 200 mL over 1 hour.)" The following statements were included in the Precautions Concerning Dosage and Administration section of the proposed package insert:

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.
- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd. Read the instructions for use and the instruction manual of the device before using the neutron beam-irradiating device.

In view of the reviews in Sections "7.R.2 Clinical positioning and efficacy" and "7.R.3 Safety" and the discussion described in the following sections, PMDA concluded that the dosage and administration

for borofalan should be "Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h." The following precautionary statements should be included in the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.
- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

7.R.5.1 Dosage regimen for borofalan

The applicant's rationale for the dosage regimen of borofalan:

Study 002 was conducted using the dosage regimen chosen based on the study results listed below, and results of Study 002 suggested the efficacy and safety of borofalan/BNCT in patients treated in this study. Therefore, the applicant has proposed the following dosage and administration for borofalan based on the dosage regimen used in Study 002: "Usually, for adults, a single dose of 500 mg/kg of borofalan (^{10}B) is administered as an intravenous infusion over 3 hours, at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during the last 1 hour. Irradiation of neutron beams to the cancer area is started at 2 hours after the start of intravenous infusion. The intravenous infusion is terminated at the end of irradiation. (In a patient weighing 60 kg, 800 mL of Steboronine solution is intravenously infused over 2 hours, followed by intravenous infusion of 200 mL over 1 hour.)" The device to be used for neutron beam irradiation will be specified in the Precautions Concerning Dosage and Administration section.

- PK data of boron obtained from single-dose studies in rats, etc., were used to estimate boron concentration in whole blood[23)] in humans receiving a single intravenous administration of borofalan at the rate of 200 mg/kg/h during the first 2 hours then at 100 mg/kg/h. Based on the results, it was estimated that boron concentration in whole blood from 2 to 3 hours after the start of administration was maintained roughly at 20 ppm, a concentration necessary for obtaining the therapeutic effect of borofalan/BNCT.

- In Study 001, boron concentration in whole blood was >20 ppm when a single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours and then at 100 mg/kg/h [see Section 6.2.1.1].

- Borofalan/BNCT was well tolerated in Study 001.

No clinical data are available on the efficacy and safety of borofalan in combination with other antineoplastic agents. This will be mentioned in the Precautions Concerning Dosage and Administration section.

[23)] The boron concentration in whole blood thus estimated was roughly the same as that estimated from PK parameters of boron in humans receiving borofalan (*Appl Radiat Isot*. 2004;61:1095-100, etc.)

PMDA's view:
No dosage regimens other than that used in Study 002 were investigated in clinical studies, leaving room for further investigations. This being said, PMDA largely accepted the rationale presented by the applicant, because Study 002 demonstrated the clinical usefulness of borofalan at the following dosage regimen: (a) Borofalan was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours and then at 100 mg/mg/h, and (b) the tumor was irradiated with a single dose of neutron beam using BNCT30 for a maximum of 60 minutes starting at 2 hours after the start of administration of borofalan. The Precautions Concerning Dosage and Administration section of the proposed package insert includes a statement that the instructions for use and the instruction manual for the neutron beam-irradiating device must be read before administering borofalan. This statement is unnecessary because this is a common caution not requiring special mention in the treatment with borofalan.

Based on the above, the dosage and administration of borofalan/BNCT should be "Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h." Also, the following precautionary statements should be included in the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.
- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

7.R.6 Post-marketing investigations

The applicant's explanation about the plan of post-marketing investigations:
In order to evaluate the safety, etc., of borofalan in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients treated with borofalan.

The safety specification of the surveillance includes events requiring caution in treatment with borofalan/BNCT (dysphagia, brain abscess, radiation skin injury, cataract, crystal urine, arterial haemorrhage [carotid haemorrhage associated with tumor shrinkage/necrosis], osteoradionecrosis/osteomyelitis, eye disorder, and central nervous system injuries), as well as the safety in patients with renal impairment and patients with cardiac impairment.

The target sample size was set at 100 patients treated with borofalan/BNCT based on the incidence, in Studies 002 and 001, of events included in the safety specification of the surveillance.

The observation period was set at 3 years from the start of administration of borofalan, based on the time to onset, in Studies 002 and 001, of events included in the safety specification of the surveillance, and based on published reports (*Appl Rad Isot*. 2015;106:202-6, *Int J Rad Oncol Biol Phys*. 2012;82:e67-75, etc.).

PMDA's view:
Because of the extremely limited safety information available for Japanese patients treated with borofalan, the applicant should conduct post-marketing surveillance covering all borofalan-treated patients for a certain period after the market launch, to collect safety information promptly without bias, and to provide safety information thus obtained to healthcare professionals without delay.

Based on the review in Section "7.R.3 Safety," safety specification of the surveillance should include dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, and carotid haemorrhage.

The planned sample size and the observation period should be reconsidered based on the incidence of events to be included in safety specification of the surveillance.

7.2 Adverse events etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Section "7.1 Evaluation data." The major non-fatal adverse events are summarized below.

7.2.1 Japanese phase I study (Study 001)

Adverse events were observed in 6 of 6 patients (100%) in the 10 Gy-Eq. group and in 3 of 3 patients (100%) in the 12 Gy-Eq. group. Adverse events for which a causal relationship to borofalan/BNCT could not be ruled out were observed in 6 of 6 patients (100%) in the 10 Gy-Eq. group and in 3 of 3 patients (100%) in the 12 Gy-Eq. group. The following adverse events occurred with an incidence of ≥50% in either group:

The 10 Gy-Eq. group:

Malaise, haematuria, and alopecia in 6 patients (100%) each, blood prolactin abnormal in 5 patients (83.3%), face oedema, amylase increased, C-reactive protein increased, hyperglycaemia, decreased appetite, and hypertension in 4 patients (66.7%) each, constipation, nausea, stomatitis, pyrexia, radiation skin injury, lymphocyte count decreased, hypoalbuminaemia, and proteinuria in 3 patients (50.0%) each.

The 12 Gy-Eq. group:

Hypoalbuminaemia and haematuria in 3 patients (100%) each, nausea, stomatitis, application site erythema, face oedema, malaise, conjunctivitis, amylase increased, blood prolactin abnormal, C-reactive protein increased, lymphocyte count decreased, hyponatraemia, decreased appetite, pharyngeal inflammation, laryngeal inflammation, and alopecia in 2 patients (66.7%) each.

A serious adverse event was observed in 1 of 6 patients (16.7%) in the 10 Gy-Eq. group, with no serious adverse events in the 12 Gy-Eq group. The serious adverse event was dysphagia in 1 patient (16.7%). Its causal relationship to borofalan/BNCT could not be ruled out.

There were no adverse events leading to discontinuation of borofalan/BNCT.

7.2.2 Japanese phase II study (Study 002)

Adverse events were observed in 21 of 21 patients (100%). Adverse events for which a causal relationship to borofalan/BNCT could not be ruled out were observed in 21 of 21 patients (100%). Adverse events with an incidence of ≥30% were alopecia in 19 patients (90.5%), amylase increased in 18 patients (85.7%), nausea in 17 patients (81.0%), dysgeusia in 15 patients (71.4%), parotitis and decreased appetite in 14 patients (66.7%) each, stomatitis in 13 patients (61.9%), vomiting in 10 patients (47.6%), malaise, thirst, and radiation skin injury in 9 patients (42.9%) each, conjunctivitis and sialoadenitis in 7 patients (33.3%) each.

A serious adverse event was observed in 1 of 21 patients (4.8%). The serious adverse event was brain abscess in 1 patient (4.8%), and its causal relationship to borofalan/BNCT could not be ruled out.

There were no adverse events leading to discontinuation of borofalan/BNCT.

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

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

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

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

The new drug application data (CTD 5.3.5.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies were generally conducted in compliance with GCP. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings requiring corrective action in a study site and by the sponsor, although the findings did not significant affect the overall evaluation of the clinical studies, it was notified to the head of the study site and the sponsor to seek improvement.

Findings requiring corrective action:

<u>Study site</u>

- Insufficient description in the contract document regarding study implementation
- The head of the study site did not submit the written information to the Institutional Review Board in advance.
- The Institutional Review Board reviewed the appropriateness of study conduct without receiving the written information.

- The investigator or other members of the study site neither provided a written explanation to, nor obtained consent from, a patient before enrollment, because the investigator or other members of another study site had already obtained consent from the patient after providing an overall explanation of the study.

Sponsor

- The sponsor did not ask the investigator to prepare the written information.
- The sponsor did not submit the written information to the head of the study site in advance.
- Insufficient description in the contract document regarding study implementation.

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

On the basis of the data submitted, PMDA has concluded that borofalan/BNCT has a certain level of efficacy in the treatment of unresectable, locally advanced or locally recurrent head and neck cancer, and that borofalan/BNCT has acceptable safety in view of its benefits. In borofalan/BNCT, neutron beam is irradiated from outside the body to borofalan, and the irradiated borofalan releases alpha rays and lithium nuclei, which have cytocidal effects. Borofalan/BNCT is clinically meaningful because it offers a treatment option for patients with unresectable, locally advanced or locally recurrent head and neck cancer. In addition, the indication, post-marketing investigations, etc., should be further reviewed.

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

Review Report (2)

February 5, 2020

Product Submitted for Approval

Brand Name	Steboronine 9000 mg/300 mL for Infusion
Non-proprietary Name	Borofalan (^{10}B)
Applicant	Stella Pharma Corporation
Date of Application	October 15, 2019

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 Clinical positioning and efficacy

In the Japanese phase II study (Study 002) in (a) patients with post-CRT or -RT unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma, the response rate [90% CI] was 71.4% [51.3%, 86.8%] (15 of 21 of patients).

As a result of its review on Section "7.R.2 Clinical positioning and efficacy" of the Review Report (1), PMDA concluded that borofalan has shown a certain level of efficacy in patients with unresectable, locally advanced or locally recurrent head and neck cancer and that borofalan/BNCT is positioned as a treatment option for these patients, taking account of the above response rate and the following:

- Localized lesions in patients with unresectable, locally advanced or locally recurrent head and neck cancer may cause various pathologies such as dysphagia, malnutrition, airway constriction, aspiration, and fistulation, thereby severely reducing their quality of life (QOL). Locally controlling the lesions is clinically meaningful.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review on Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that special attention should be paid to the following adverse events when administering borofalan/BNCT

to patients with unresectable, locally advanced or locally recurrent head and neck cancer: dysphagia, brain abscess, skin disorder, crystal urine, cataract, and carotid haemorrhage.

PMDA also concluded that although attention should be paid to the above-mentioned adverse events during treatment with borofalan/BNCT, the treatment is tolerable if adverse events are monitored and controlled and other appropriate actions are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Indication

As a result of the review on Section "7.R.4 Indications" of the Review Report (1), PMDA concluded that the indication should be "unresectable, locally advanced or locally recurrent head and neck cancer," that details of patients treated in Study 002 should be described in the Clinical Studies section of the package insert, and that the following precautionary statements should be included in the Precautions Concerning Indication section:

Precautions Concerning Indication

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.
- The efficacy and safety of borofalan as adjuvant therapy have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the above wording for Indication and include the above precautionary statements in the Indication and Precautions Concerning Indication section. The applicant agreed.

1.4 Dosage and administration

As a result of the review on Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the dosage and administration for borofalan should be "Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h," and that the following precautionary statements should be included in the Precautions Concerning Dosage and Administration section:

Precautions Concerning Dosage and Administration

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.
- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the above wording for Dosage and Administration and include the above precautionary statements in the Precautions Concerning Dosage and Administration section. The applicant agreed.

1.5 Risk management plan (draft)

In order to evaluate the safety, etc., of borofalan in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients treated with borofalan, with the planned sample size of 100 patients receiving borofalan/BNCT and the observation period of 3 years.

As a result of the review on Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA concluded that the applicant should conduct post-marketing surveillance covering all borofalan-treated patients for a certain period after the market launch, to collect safety information promptly without bias, and to provide safety information thus obtained to healthcare professionals without delay. Also, PMDA concluded that the surveillance plan should be designed as follows:

- Safety specification of the surveillance should include dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, and carotid haemorrhage.

- The planned sample size and the observation period should be reconsidered based on the incidence of events to be included in safety specification of the surveillance.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. At the same time, the following comment was raised by the expert advisors:

- The clinical studies have provided only limited information on the safety after a certain period of time following the administration of borofalan/BNCT, and late toxicity is a known risk of existing RT. Therefore, information on late toxicity should also be collected in the surveillance.

Based on the above discussion, PMDA instructed the applicant to revise the surveillance plan.

The applicant's response:

- Safety specification will include dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, carotid haemorrhage, and late toxicity.

- The planned sample size and the observation period will be 150 patients and 3 years, respectively, based on the feasibility and the incidence of events included in the safety specification.

PMDA accepted the explanation of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety specification presented in Table 20, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 21 and 22.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Dysphagia • Brain abscess • Severe skin disorder • Crystalluria • Cataract • Carotid haemorrhage	None	• Late toxicity
Efficacy specification		
None		

Table 21. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case survey)	None	• Disseminate data gathered through early post-marketing phase vigilance

Table 22. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety, etc., of borofalan in clinical use after the market launch
Survey method	All-case surveillance
Population	All patients receiving borofalan
Observation period	3 years
Planned sample size	150 (safety analysis population consisting of patients receiving borofalan/BNCT)
Main survey items	Safety specification: Dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, carotid haemorrhage, and late toxicity. Other main survey items: Patient characteristics (age, sex, disease stage, past illness, concurrent illness, etc.), use of borofalan, neutron beam irradiation, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and dosage and administration (modified from the proposed text) with the approval conditions shown below, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is properly disseminated after the market launch, and provided that the product is used properly under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy and radiotherapy at a medical institution that can adequately respond to emergencies. 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. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Unresectable, locally advanced or locally recurrent head and neck cancer

Dosage and Administration

Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h.

Approval Conditions

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

2. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Warning

The product should be administered only to patients considered to be eligible for the treatment with the product by a physician with sufficient knowledge and experience in cancer chemotherapy and radiotherapy at a medical institution capable of emergency response. Prior to treatment, patients or their families should be thoroughly informed of the potential risks and benefits of the treatment and provide consent.

Contraindications

1. Patients with a history of hypersensitivity to any ingredient of the product

2. Patients with circumferential tumor infiltration to the carotid artery (Carotid haemorrhage may occur.)

Precautions Concerning Indication

1. The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.
2. The efficacy and safety of borofalan as adjuvant therapy have not been established.

3. Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.

2. Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

Appendix

List of Abbreviations

^{14}C-labeled borofalan	^{14}C-labeled borofalan (^{10}B)
ALT	alanine aminotransferase
AMP	adenosine monophosphate
Application	Marketing application
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BNCT	boron neutron capture therapy
BNCT30	NeuCure BNCT System
Borofalan	borofalan (^{10}B)
Borofalan/BNCT	BNCT with borofalan
Cetuximab	cetuximab (genetical recombination)
CheckMate 141 study	Study ONO-4538-11/CA209141
CHO cells	Chinese hamster ovary cells
CI	confidence interval
CR	complete response
CrCL	creatinine clearance
CRT	chemoradiotherapy
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
efflux ratio	the ratio of permeability coefficient in the direction of secretion to that in the direction of absorption
eGFR	estimated glomerular filtration rate
EXTREME study	Study EMR62202-002
GC	gas chromatography
Gy-Eq.	gray equivalent
hERG	human *ether-a-go-go*-related gene
HLGT	high level group term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q3A Guideline	"Revision of the Guideline on Impurities in New Drug Substances" (PFSB/ELD Notification No. 1216001, dated December 16, 2002)
ICH Q3B Guideline	"Revision of the Guideline on Impurities in New Drug Products" (PFSB/ELD Notification No. 0624001, dated June 24, 2003)
Ig	immunoglobulin
IR	infrared spectrophotometry
JP	Japanese Pharmacopoeia
LAT-1	L-type amino acid transporter-1
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
NE	not evaluable
Nivolumab	nivolumab (genetical recombination)
NMR	nuclear magnetic resonance spectroscopy
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics

PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
QD	quaque die
QTc	QT interval corrected
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SD	stable disease
SOC	system organ class
Study 001	Study WW2P2040E001/SPM-011-JHN001
Study 002	Study WW2P2040E004/SPM-011-JHN002
UV/VIS	ultraviolet/visible spectrophotometry