

Report on the Deliberation Results

September 8, 2020

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

Brand Name	Akalux IV Infusion 250 mg
Non-proprietary Name	Cetuximab Sarotalocan Sodium (Genetical Recombination) (JAN*)
Applicant	Rakuten Medical Japan K.K.
Date of Application	March 26, 2020

Results of Deliberation

In its meeting held on September 4, 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 classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.
3. The applicant is required to provide data on the efficacy and safety of a treatment procedure with the product from the ongoing phase III study in patients with unresectable locally recurrent head and neck cancer to healthcare professionals in an appropriate manner.
4. The applicant is required to take necessary measures to ensure that the product is used only by physicians who have been trained for the treatment procedure with the product and have sufficient knowledge and experience in the treatment procedure.

**Japanese Accepted Name (modified INN)*

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Review Report

August 19, 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).

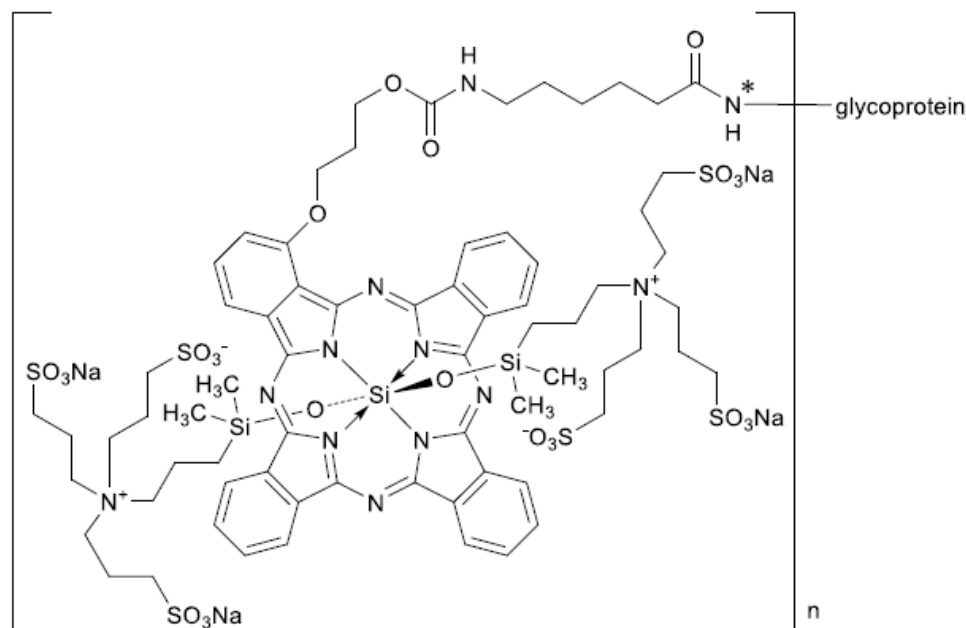
Brand Name	Akalux IV Infusion 250 mg
Non-proprietary Name	Cetuximab Sarotalocan Sodium (Genetical Recombination)
Applicant	Rakuten Medical Japan K.K.
Date of Application	March 26, 2020
Dosage Form/Strength	Injection: Each vial contains 250 mg of Cetuximab Sarotalocan Sodium (Genetical Recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Cetuximab Sarotalocan Sodium is an antibody-drug-conjugate (molecular weight: 156,000-158,000) consisting of tetrasodium salt of Sarotalocan (6-([3-((OC-6-13)-bis([3-[bis(3-sulfopropyl)(3-sulfonatopropyl)azaniumyl]propyl}dimethylsilanolato-κO,κO')[(phtalocyaninato(2-)-κN ²⁹ ,κN ³⁰ ,κN ³¹ ,κN ³²)-1-l]silicon}oxy)propoxy]carbonyl}amino) hexanoyl (C ₇₀ H ₉₆ N ₁₁ O ₂₄ S ₆ Si ₃ ; molecular weight: 1,752.22)) attached to an average of 2-3 Lys residues of Cetuximab.

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Structure

Major sarotalocan sodium binding sites: K145 in L-chain, K215 in H-chain, K292 in H-chain, K416 in H-chain

Structural formula of sarotalocan sodium site:



n = 2 to 3

*Nitrogen atom of Lys residue in the antibody moiety

Items Warranting Special Mention

SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 4 of 2019 [31 *yaku*]; PSEHB/PED Notification No. 0408-1 dated April 8, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

The product is subjected to Conditional Early Approval System (PSEHB/PED Notification No. 0529-7 dated May 29, 2020)

Reviewing Office

Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of unresectable locally advanced or recurrent head and neck cancer in combination with laser beam irradiation, 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. The occurrences of carotid arterial haemorrhage and tumour haemorrhage, swollen tongue and laryngeal oedema, infusion reaction, photosensitivity as well as severe skin disorder need to be further investigated via post-marketing surveillance.

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Indication

Unresectable locally advanced or recurrent head and neck cancer

Dosage and Administration

The usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over 2 hours or longer once daily. A laser beam is applied to the lesion 20 to 28 hours after the end of intravenous infusion.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.
3. The applicant is required to provide data on the efficacy and safety of a treatment procedure with the product from the ongoing phase III study in patients with unresectable locally recurrent head and neck cancer to healthcare professionals in an appropriate manner.
4. The applicant is required to take necessary measures to ensure that the product is used only by physicians who have been trained for the treatment procedure with the product and have sufficient knowledge and experience in the treatment procedure.

Review Report (1)

July 3, 2020

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	Aka-lux Injection 250 mg
Non-proprietary Name	Cetuximab Sarotalocan Sodium (Genetical Recombination)
Applicant	Rakuten Medical Japan K.K.
Date of Application	March 26, 2020
Dosage Form/Strength	Injection: Each vial contains 250 mg of Cetuximab Sarotalocan Sodium (Genetical Recombination)
Proposed Indication	Recurrent head and neck cancer

Proposed Dosage and Administration

The usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over approximately 2 hours or longer once daily. Non-thermal red light (laser beam) is applied to the lesion approximately 24 ± 4 hours after the end of intravenous infusion.

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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

Cetuximab Sarotalocan Sodium (genetical recombination) (hereinafter referred to as “cetuximab sarotalocan”) in combination with laser beam irradiation (cetuximab sarotalocan/laser beam irradiation) is a treatment procedure that is expected to damage tumor cells by exciting cetuximab sarotalocan bound to epidermal growth factor receptor (EGFR) expressed on tumor cell membrane through laser beam irradiation at 690 nm with a semiconductor laser device.

Cetuximab sarotalocan is an antibody-drug conjugate (ADC) discovered by the applicant in which cetuximab (genetical recombination) (cetuximab), anti-EGFR chimeric monoclonal antibody of immunoglobulin (Ig) G1 subclass, is conjugated with a phthalocyanine derivative (silicate(4-),[2,5-dioxo-1-pyrrolidinyl 6-[[[3-[(29H,31H-phthalocyanin-1-yl)κN²⁹,κN³⁰,κN³¹,κN³²]oxy]propoxy]carbonyl]amino]hexanoato(2-)]bis[N-[3-[(hydroxy-κO)dimethylsilyl]propyl]-3-sulfo-N,N-bis(3-sulfopropyl)-1-propanaminiumato(4-)]-,sodium (1:4) [IR700 NHS ester]), a photosensitizer.

1.2 Development history, etc.

Outside of Japan, the applicant initiated a phase I/IIa study (RM-1929-101 study [Study 101]) of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck squamous cell carcinoma in June 2015.

As of May 2020, cetuximab sarotalocan has not been approved in any country or region.

In Japan, the applicant initiated a phase I study (RM-1929-102 study [Study 102]) of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck squamous cell carcinoma in March 2018.

The applicant submitted the marketing application for cetuximab sarotalocan, using data from Studies 101 and 102 as the pivotal study results.

The application for cetuximab sarotalocan was submitted using “Aka-lux Injection 250 mg” as the brand name, but it was changed to “Akalux IV Infusion 250 mg” from a viewpoint of medical safety. In addition, cetuximab sarotalocan was designated as a drug to be reviewed under the SAKIGAKE Designation System (SAKIGAKE Drug Designation No. 4 of 2019 [*31 yaku*]) with the intended indication of “head and neck cancer” in April 2019. Cetuximab sarotalocan was also subjected to as the Conditional Early Approval System for drugs (PSEHB/PED Notification No. 0529-7 dated May 29, 2020) in May 2020.

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

Cetuximab sarotalocan is an ADC in which cetuximab, anti-EGFR monoclonal antibody, is conjugated with a phthalocyanine derivative (IR700 NHS ester), which is excited by light at 690 nm, through its lysine residue.

2.1 Drug substance

Cetuximab and IR700 NHS ester are controlled as critical intermediates of the drug substance.

2.1.1 Cetuximab

Cetuximab has been registered in the master file (MF) (MF registration No. 301MF10063) by Merck Serono SA.

2.1.1.1 Generation and control of cell substrate

It is as shown in the annex.

2.1.1.2 Manufacturing process

It is as shown in the annex.

2.1.1.3 Safety evaluation of adventitious agents

In the manufacturing process of cetuximab, the following biological ingredients are used in addition to Sp2/0-Ag14 cells, host cells:

(a) Preparation of master cell bank (MCB):

Fetal bovine serum, bovine cholesterol, bovine serum albumin, and bovine transferrin produced in the US¹⁾ as well as bovine insulin of unknown origin country

(b) Preparation of working cell bank (WCB):

Fetal bovine serum, bovine serum albumin, and bovine serum lipoprotein

(c) Cell culture process:

Bovine serum albumin and bovine serum lipoprotein

Of the above raw materials, all except for materials used in preparation of MCB have been confirmed to conform to the Standards for Biological Ingredients. The raw materials used in preparation of MCB meet the conditions provided in “Handling of Drugs etc. Produced from Master Cell Banks or Master Seeds That Do Not Meet the Standards for Biological Ingredients” (Administrative Notice dated March 27, 2009) and are deemed to be eligible for use.

Purity has been tested on the MCB, WCB, and cells at the limit of *in vitro* cell age (CAL). In addition, the pre-harvest crude bulk obtained on a commercial scale was subjected to sterility, mycoplasma, *in vitro* adventitious virus, minute virus of mice, and reverse transcriptase activity tests as well as transmission electron microscopy. Within a range of parameters tested, no contamination with viral or non-viral infectious agents was noted. The sterility, mycoplasma, and *in vitro* adventitious virus tests on the pre-harvest crude bulk are specified as the in-process control tests.

The purification process was subjected to a viral clearance study using model viruses and thereby demonstrated to have a certain level of viral clearance capability (Table 1).

¹⁾ Collected before 2013, the year when the US was accredited as a country with a negligible risk of bovine spongiform encephalopathy (BSE) by the World Organisation for Animal Health (OIE).

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log ₁₀)			
	Xenotropic murine leukemia virus	Bovine viral diarrhea virus	Pseudorabies virus	Mouse minute virus
Low-pH virus inactivation	██████████	██████████	██████████	██████████
██████████ chromatography	██████████	██████████	██████████	██████████
Virus removal filtration	██████████	██████████	██████████	██████████
Overall viral reduction factor	≥18.39	≥8.85	≥17.83	8.35

2.1.1.4 Manufacturing process development

It is as shown in the annex. A supplier of cetuximab was changed in a course of the development [see Section 2.1.3.2].

2.1.1.5 Characterization

It is as shown in the annex.

2.1.1.6 Control

The proposed specifications for cetuximab include content, identification (image capillary isoelectric focusing [icIEF]), pH, glycan profile, purity (size exclusion liquid chromatography [SEC-LC] and sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE] [non-reduced and reduced]), cation exchange liquid chromatography (CEX-LC), bacterial endotoxins, microbial limit, EGFR-binding activity (enzyme-linked immunosorbent assay [ELISA] method), and assay (ultraviolet-visible spectrophotometry).

2.1.1.7 Stability

Table 2 shows major stability studies of cetuximab.

Table 2. Outline of major stability studies of cetuximab

	Number of batches	Storage condition	Period	Storage package
Long-term testing	3	5 ± 3°C	██████████ months	Polyethylene bag
Accelerated testing	3	██████████ ± ██████████ °C / ██████████ ± ██████████ %RH	██████████ months	

Under the long-term condition, no clear changes in quality attributes were observed throughout the period.

Under the accelerated condition, the following changes were observed: An increasing trend of ██████████ in ██████████, a decreasing trend of ██████████ in ██████████, a decreasing trend of ██████████ in ██████████ (██████████), a decreasing trend of ██████████ in ██████████ (██████████), and a decreasing trend of ██████████ (██████████).

On the basis of the above, the shelf life of ██████████ months has been proposed for cetuximab when stored in a polyethylene bag at 2°C to 8°C.

2.1.2 IR700 NHS ester

2.1.2.1 Characterization

IR700 NHS ester is a blue to green solid. Its general properties, including description, solubility, molar absorption coefficient, wavelength of absorption maximum, wavelength of emission maximum, thermogravimetric profile and differential scanning calorimetric profile, have been determined.

The chemical structure of IR700 NHS ester has been elucidated by infrared absorption spectrum (IR), nuclear magnetic resonance spectrum (¹H-NMR and ¹³C-NMR), and mass spectrum.

2.1.2.2 Manufacturing process

IR700 NHS ester is synthesized using [redacted] as a starting material.

The synthesis of IR700 NHS ester (each of the processes involved in [redacted]), [redacted], and [redacted] processes are identified as the critical steps, and the process control items and process control values have been established for each of the processes for synthesis of IR700 NHS ester and [redacted].

2.1.2.3 Control

The proposed specifications for IR700 NHS ester include description, identification (IR and liquid chromatography [LC]), purity (purity [LC], related substances [LC], elemental impurities [inductively coupled plasma-mass spectrometry]), residual solvents (LC and gas chromatography [GC]), water content, and bacterial endotoxins.

2.1.2.4 Stability

Table 3 shows major stability studies of IR700 NHS ester.

Table 3. Outline of major stability studies of IR700 NHS ester

Testing	Number of batches (scale)	Storage condition	Storage period	Storage package
Long-term testing	3 (pilot)	[redacted] ± [redacted] °C	1 batch: [redacted] months 2 batches: [redacted] months	Brown glass container + aluminum-laminated bag + high density polyethylene container

On the basis of the above, [redacted] of [redacted] months has been proposed for IR700 NHS ester when filled in a brown glass container, placed in an aluminum-laminated bag, packaged in a high density polyethylene container, and stored at [redacted] °C, [redacted]. Long-term testing with commercial-scale batches is also currently ongoing.

2.1.3 Cetuximab sarotalocan sodium (genetical recombination)

2.1.3.1 Manufacturing process

The manufacturing process of the drug substance consists of processes for [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and filling/testing/storage.

██████████, ██████████, ██████████, and ██████████ are identified as the critical steps.

The manufacturing process of the drug substance is currently under process validation on a commercial scale.

2.1.3.2 Manufacturing process development

Main changes on the manufacturing process in a course of the development of the drug substance are as shown below (relevant manufacturing processes are denoted as Process A, Process B, and proposed process):

- From Process A to Process B: ██████████, manufacturing site, ██████████, ██████████, ██████████, ██████████, ██████████, and others.
- From Process B to proposed process: ██████████, change in ██████████ during manufacture, and others.

In Studies 101 and 102, the Process A formulation has been used. In association with the above process changes, comparability evaluation on quality attributes was conducted and has demonstrated comparability between the pre- and post-change drug substances.

The quality-by-design (QbD) technique has been applied to development of the manufacturing process [see Section 2.3].

2.1.3.3 Characterization

2.1.3.3.1 Structure and characterization

Table 4 shows contents of characterization performed on the drug substance.

Table 4. Properties of drug substance characterized

Primary structure/ higher-order structure	Posttranslational modification (oxidation, deamidation), DAR, ██████████, ██████████, particle size, and thermostability
Physicochemical properties	Molecular weight, charge variants, size variants, ██████████, and insoluble particulate matter
Carbohydrate structure	N-linked glycan profile
Biological properties	Binding affinity to EGFR
	Cell growth inhibition, EGFR signaling inhibition
	ADCC activity
	██████████ by ██████████

Characterization results on the biological properties were as shown below. Evaluation on biological activities related to antibody also included cetuximab, which was used as the antibody moiety of the drug substance, as a comparator.

- ██████████ demonstrated that the drug substance and cetuximab had a similar binding affinity to EGFR.
- Evaluation in human skin squamous cell carcinoma A431 cell line and human pharyngeal carcinoma FaDu cell line demonstrated that the drug substance and cetuximab inhibited EGFR signaling to the same extent.
- Evaluation in FaDu cell line demonstrated that the drug substance and cetuximab inhibited cell growth to the same extent.

- Evaluation in human T-cell leukemia Jurkat cell line and A431 cell line demonstrated that the drug substance had weaker antibody dependent cellular cytotoxicity (ADCC) than cetuximab did.
- Evaluation in human pancreatic adenocarcinoma BxPC3 cell line demonstrated that cetuximab sarotalocan inhibited the cell growth when a laser beam at 690 nm was applied.

2.1.3.3.2 Product-related substances/Product-related impurities

On the basis of the characterization results in Section 2.1.3.3.1, a Related Substance A was deemed as a product-related substance. In addition, Impurities B, C, D, and E were deemed as product-related impurities. Of the product-related impurities, Impurities B, C, and E are controlled by the specifications of the drug substance and drug product, and Impurity D is controlled by the specifications of the drug product.

2.1.3.3.3 Process-related impurities

Bacterial endotoxins, bioburden, and Impurities F, G, H, and I are deemed as process-related impurities. Bacterial endotoxins are controlled by the specifications of the drug substance and drug product; bioburden is controlled by the specifications of the drug substance; and Impurity F is controlled by in-process control tests for the drug substance. In addition, Impurities G, H, and I are controlled as shown in the annex.

2.1.3.4 Control of drug substance

The proposed specifications for the drug substance include description, content, identification (SEC-LC), pH, purity (SEC-LC [wavelength, [REDACTED] and [REDACTED] nm]), drug-to-antibody ratio (DAR), bacterial endotoxins, microbial limit, potency ([REDACTED]), binding affinity to EGFR (ELISA method), and assay (SEC-LC).

2.1.3.5 Stability of drug substance

Table 5 shows major stability studies of the drug substance.

Table 5. Outline of major stability studies of drug substance

	Manufacturing process	Number of batches	Storage condition	Period	Storage package
Long-term testing	Process B	2	5 ± 3°C	[REDACTED] months	Plastic bag*
	Proposed process	1			
Accelerated testing	Process B	2	[REDACTED] ± [REDACTED]°C/[REDACTED] ± [REDACTED]%RH	[REDACTED] months	
	Proposed process	1			
Stress testing	Process B	1	[REDACTED] ± [REDACTED]°C/[REDACTED] ± 5%RH	[REDACTED] months	

* Bag made of a multilayer film including an inner low density polyethylene layer

Under the long-term condition, no changes in quality attributes were observed throughout the period.

Under the accelerated condition, the following changes were observed: A decreasing trend of [REDACTED] and an increase of [REDACTED] in [REDACTED], a decreasing trend of [REDACTED], a decreasing trend of [REDACTED] in capillary electrophoresis sodium dodecyl sulfate (CE-SDS) ([REDACTED]), a decreasing trend of [REDACTED] in [REDACTED] ([REDACTED]), a decreasing trend of [REDACTED], a decreasing trend of [REDACTED] ([REDACTED]), and an increase of [REDACTED].

Under the stress condition, the following changes were observed in addition to changes observed under the accelerated condition: A decreasing trend of [REDACTED], a decrease of [REDACTED] in [REDACTED], an increase of [REDACTED] and an increasing trend of [REDACTED], a decrease of [REDACTED] in [REDACTED] ([REDACTED]), a decrease of [REDACTED] in [REDACTED] ([REDACTED]), a decrease of [REDACTED] ([REDACTED]), and a decrease of [REDACTED] ([REDACTED]).

Because the drug substance is photolabile, no photostability testing has been conducted.

On the basis of the above, the shelf life of [REDACTED] months has been proposed for the drug substance when stored in a plastic bag as the primary container and in [REDACTED] at 2°C to 8°C, under protection from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is presented in a brown glass vial (50 mL) as an aqueous injection containing 250 mg (protein amount) of the drug substance per 50 mL of the drug solution. The drug product contains disodium hydrogen phosphate anhydrous, monobasic sodium phosphate monohydrate, trehalose hydrate, polysorbate 80, and water for injection as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising sterile filtration, filling, labeling/packaging, and testing/storage.

[REDACTED] and [REDACTED] are identified as the critical steps.

The manufacturing process of the drug product is currently under process validation on a commercial scale.

2.2.3 Manufacturing process development

Main changes on the manufacturing process in a course of the development of the drug product are as shown below. In addition, both changes were made at the same time when changes were made on the manufacturing process of the drug substance, and comparability between the pre- and post-change drug products has been demonstrated [see Section 2.1.3.2] (relevant manufacturing processes are denoted as Process A, Process B, and proposed process as done for the changes on the manufacturing process of the drug substance):

- From Process A to Process B: Manufacturing site, [REDACTED], [REDACTED], [REDACTED], and others.
- From Process B to proposed process: [REDACTED], [REDACTED], and others.

The QbD technique has been applied to development of the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (SEC-LC and peptide mapping), pH, osmolarity, purity (SEC-LC [wavelength, [REDACTED] and [REDACTED] nm] and CE-

- Development of control method:

On the basis of the process knowledge including results from the above process characterization, the quality properties of the product have been confirmed to be appropriately controlled by a combination of control of process parameters, in-process control, and specifications [for control of product-related and process-related impurities, see Sections 2.1.1.5 and 2.1.3.3.2 as well as 2.1.1.5 and 2.1.3.3.3, respectively].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the quality of the drug substance is appropriately controlled. For the drug product, the long-term testing results have not been submitted [see Section 2.2.5], and thus PMDA's final conclusion on the quality of the drug product is described in the Review Report (2).

For the product, data related to the MF were separately submitted by the MF registrant, and results from PMDA's review on the MF are as shown in the annex.

2.R.1 Novel excipients

The drug product contains a new excipient trehalose hydrate in an amount exceeding that of the previous uses for intravenous injection.

2.R.1.1 Specifications and stability

PMDA concluded that the specifications and stability of trehalose hydrate to be used in the drug product had no problem because it conforms to requirements specified in the Japanese Pharmacopoeia.

2.R.1.2 Safety

On the basis of the submitted data, PMDA concluded that trehalose hydrate was unlikely to raise safety problems at the amount proposed for the drug product.

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

3.1 Primary pharmacodynamics

3.1.1 Binding affinity to EGFR (CTD 4.2.1.1.1 and 4.2.1.1.9)

The binding affinity of cetuximab sarotalocan and cetuximab to human EGFR (recombinant protein) was investigated by the ELISA method. The 50% effective concentration (EC_{50}) values (mean \pm standard deviation [SD]) of cetuximab sarotalocan and cetuximab were 20.6 ± 2.6 (n = 3) and 22.8 ± 2.1 ng/mL (n = 5), respectively.

The binding affinity of cetuximab sarotalocan and cetuximab to human EGFR (recombinant protein) was investigated by reflectometric interference spectroscopy. The binding dissociation constant (K_D) values (mean \pm SD, n = 3) of cetuximab sarotalocan and cetuximab were 107 ± 20 and 582 ± 112 pmol/L, respectively.

3.1.2 Damage on cell membrane (CTD 4.2.1.1.2)

Endogenously EGFR expressing A431 cell line and murine embryo fibroblast NIH/3T3 cell line with HER2 being forced to express were co-cultured to investigate damage on cell membrane given by cetuximab sarotalocan/laser beam irradiation using deoxyribonucleic acid (DNA) staining with cell membrane-impermeable ethidium homodimer-1 as an indicator. At 90 minutes after laser beam irradiation, DNA was stained only in A431 cell line, indicating that cell membrane of this cell line was damaged.

3.1.3 Inhibition against EGFR autophosphorylation (CTD 4.2.1.1.12)

EGFR undergoes autophosphorylation upon binding of epidermal growth factor (EGF), EGFR ligand. Against such EGFR autophosphorylation, inhibitory activity of cetuximab sarotalocan and cetuximab at 0.05, 0.5, 5, and 50 µg/mL was investigated by the ELISA method, using endogenously EGFR expressing A431 cell line and FaDu cell line cultured in the presence of cetuximab sarotalocan or cetuximab. Table 7 shows results on inhibitory activity of cetuximab sarotalocan and cetuximab against EGFR autophosphorylation upon EGF-binding.

Table 7. Inhibitory activity of cetuximab sarotalocan and cetuximab against EGFR autophosphorylation

Cell line	Drug (µg/mL)	Percentage of phosphorylated EGFR* (%)	
A431	Cetuximab sarotalocan	50	10.521 ± 0.249
		5	25.759 ± 1.660
		0.5	53.845 ± 11.181
		0.05	94.931 ± 3.589
	Cetuximab	50	9.528 ± 0.706
		5	24.197 ± 0.909
		0.5	67.954 ± 5.475
		0.05	95.249 ± 2.968
FaDu	Cetuximab sarotalocan	50	8.357 ± 0.621
		5	10.036 ± 0.553
		0.5	21.212 ± 1.551
		0.05	73.646 ± 5.031
	Cetuximab	50	7.976 ± 0.889
		5	11.798 ± 1.232
		0.5	25.922 ± 1.086
		0.05	76.889 ± 9.777

Mean ± SD; n = 3; * Percentage of phosphorylated EGFR with respect to that without a drug (100)

3.1.4 ADCC activity (CTD 4.2.1.1.10)

The ADCC activity of cetuximab sarotalocan and cetuximab on A431 cell line was investigated using Jurkat cell line transfected with luciferase gene as effector cells, in which the luciferase activity was used as an indicator. The EC₅₀ values (mean [range], n = 3) of cetuximab sarotalocan and cetuximab were 15.45 (14.50-16.46) and 10.91 (10.17-11.71) ng/mL, respectively.

3.1.5 Growth inhibition against malignant tumor cell lines

3.1.5.1 *In vitro* (CTD 4.2.1.1.6, 4.2.1.1.7, and 4.2.1.1.11)

The growth inhibition of cetuximab sarotalocan and cetuximab against FaDu cell line was investigated using the amount of viable cell-derived adenosine triphosphate (ATP) as an indicator. The EC₅₀ values (mean [range], n = 3) of cetuximab sarotalocan and cetuximab were 35.73 (29.25-43.64) and 42.66 (37.30-48.79) ng/mL, respectively.

The growth inhibition of cetuximab sarotalocan in combination with laser beam irradiation at 690 nm and 8 or 32 J/cm² against endogenously EGFR expressing BxPC3 cell line was investigated using DNA staining with an asymmetric cyanine dye as an indicator. The EC₅₀ values (individual values, n = 2) of cetuximab sarotalocan in combination with laser beam irradiation at 690 nm and (a) 8 and (b) 32 J/cm² were (a) 23.63 and 33.46 ng/mL as well as (b) 6.58 and 8.09 ng/mL.

An EGFR expression level and growth inhibition of cetuximab sarotalocan at 10 µg/mL in combination with laser beam irradiation at 690 nm against A431, FaDu, and BxPC3 cell lines as well as human squamous cell carcinoma SCC-15 cell line were investigated by flow cytometry. Table 8 shows EGFR expression level on the cell surface and ED₅₀ value with a laser beam at 690 nm.

Table 8. EGFR expression level on and growth inhibition of cetuximab sarotalocan against each cell line

Cell line	EGFR expression level* ¹	ED ₅₀ value (J/cm ²)* ²
A431	1,574,000	1.39, 1.48
FaDu	608,000	6.33, 7.74
BxPC3	408,000	7.78, 7.68
SCC15	461,000	13.32, 14.04

*¹ Value quantitatively reflecting measured antibody binding capacity; *² n = 2 (individual values)

3.1.5.2 *In vivo* (CTD 4.2.1.1.13)

Using nude mice transplanted with BxPC3 cell line in the pancreas (n = 5/group), tumor growth inhibition of cetuximab sarotalocan/laser beam irradiation was investigated. At 2 weeks after implantation, cetuximab sarotalocan at 100 µg was intravenously administered. At 24 hours after administration of cetuximab sarotalocan, the tumor was surgically exposed and irradiated at 250 J/cm² with 690 nm wavelength laser beam at 150 mW/cm², and the tumor area was calculated. Compared with the control group (administration of phosphate buffer followed by laser beam irradiation), the cetuximab sarotalocan/laser beam irradiation group showed statistically significant tumor growth inhibition (Figure 1).

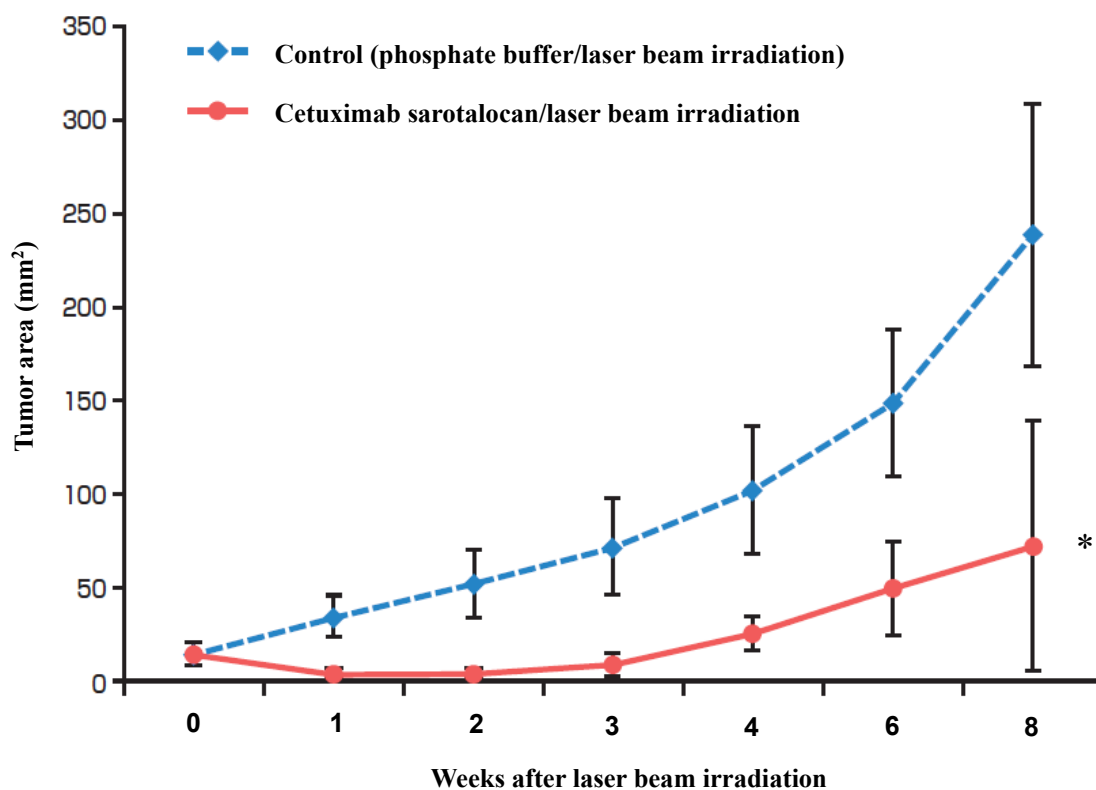


Figure 1. Tumor growth inhibition of cetuximab sarotalocan/laser beam irradiation in nude mice transplanted with BxPC3 cell line in the pancreas

n = 5; * $P < 0.001$ vs. control group (Student's t test)

3.2 Safety pharmacology

In a single intravenous dose toxicity study in cynomolgus monkeys, effects of cetuximab sarotalocan at 40 and 80 mg/kg on the central nervous, cardiovascular, and respiratory systems were investigated [see Section 5.1]. No effects of cetuximab sarotalocan were observed.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about non-clinical pharmacology findings of cetuximab sarotalocan was acceptable except for matters reviewed in the following section.

3.R.1 Mechanism of action of cetuximab sarotalocan/laser beam irradiation and efficacy

The applicant's explanation about the mechanism of action of cetuximab sarotalocan/laser beam irradiation and the efficacy in the treatment of head and neck cancer:

Cetuximab sarotalocan is an ADC in which cetuximab, anti-EGFR chimeric monoclonal antibody of IgG1 subclass, is conjugated with a phthalocyanine derivative, a photosensitizer through its lysine residue. Although cetuximab sarotalocan has weaker ADCC activity than cetuximab [see Section 3.1.4], it binds to EGFR [see Section 3.1.1] and inhibits EGFR autophosphorylation [see Section 3.1.3] as with cetuximab, and thus it may also inhibit tumor growth independently of laser beam irradiation as with cetuximab. Because damage on the cell membrane occurred immediately after laser beam irradiation [see Section 3.1.2], tumor growth inhibition of cetuximab sarotalocan independent of laser beam irradiation is considered negligible in the mechanism of action. Cetuximab sarotalocan is accordingly considered to exert a cytotoxic effect as follows: It binds to EGFR expressed on the cell membrane of

tumor cells [see Section 3.1.1] and then involves a photochemical reaction of the phthalocyanine derivative excited by a laser beam at 690 nm (*ACS Cent Sci.* 2018;4;1559-69), which damages the cell membrane of tumor cells [see Section 3.1.2].

In consideration of the following matters in addition to the above mechanism of action, the efficacy of cetuximab sarotalocan/laser beam irradiation in the treatment of head and neck cancer can be expected: EGFR expressed on head and neck cancer in $\geq 90\%$ of the patients (*J Clin Oncol.* 2015;33:3305-13); cetuximab sarotalocan/laser beam irradiation inhibited growth of cell lines derived from human head and neck cancer [see Sections 3.1.5.1 and 3.1.5.2]; and cetuximab sarotalocan/laser beam irradiation is a local treatment procedure.

PMDA's view:

PMDA largely accepted the above applicant's explanation. The cytotoxic effect of cetuximab sarotalocan dependent on laser beam irradiation at 690 nm is considered to be exerted by a novel mechanism of action, but the detailed mechanism at a molecular level mostly remains to be elucidated. Because information on the mechanism of action including laser beam-independent contribution of cetuximab sarotalocan to tumor growth inhibition may be useful in predicting the efficacy of cetuximab sarotalocan in clinical use, the applicant should continue collecting the concerned information and, if a new finding becomes available, provide the information to healthcare professionals in an appropriate manner.

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

Pharmacokinetics (PK) of cetuximab sarotalocan in animals was investigated using monkeys and others.

4.1 Analytical method

4.1.1 Measurement method

Serum concentrations of cetuximab sarotalocan and silicate(5-),bis[*N*-[3-[(hydroxy- κO)dimethylsilyl]propyl]-3-sulfo-*N,N*-bis(3-sulfopropyl)-1-propanaminiumato(4-)] [6-[[[3-(29*H*,31*H*-phthalocyanin-1-yl κN^{29} , κN^{30} , κN^{31} , κN^{32})oxy]propoxy]carbonyl]amino]hexanoato(3-)]-,sodium (1:5) (IR700 carboxylate) were determined by [REDACTED], and their lower limits of quantification were 2.00 and 0.0233 $\mu\text{g/mL}$, respectively.

4.2 Absorption

4.2.1 Single-dose study

A single dose of cetuximab sarotalocan at 40 or 80 mg/kg was intravenously administered over 2 hours to male and female monkeys to measure serum concentrations of cetuximab sarotalocan and IR700 carboxylate (Table 9). No clear differences were observed in PK parameters of either cetuximab sarotalocan or IR700 carboxylate between male and female monkeys. In addition, the serum concentrations of IR700 carboxylate at either dose were below the lower limit of quantification values during a period from 4 to 8 hours post-dose.

Table 9. PK parameters of cetuximab sarotalocan and IR700 carboxylate (male and female monkeys, single intravenous administration)

Analyte	Dose (mg/kg)	Sex	n	C _{max} (µg/mL)	AUC _{last} (µg•h/mL)	t _{1/2} (h)	CL (mL/h/kg)	V _d (mL/kg)
Cetuximab sarotalocan	40	Male	3	887.7 ± 92.7	16,211 ± 3,403	41.7 ± 5.28	2.45 ± 0.48	145.6 ± 18.2
		Female	3	732.0 ± 35.8	11,645 ± 394.5	35.7 ± 3.49	3.34 ± 0.08	172.2 ± 20.8
	80	Male	5	1,704 ± 173.6	38,249 ± 5,386	57.0 ± 16.3	2.07 ± 0.27	169.4 ± 47.7
		Female	5	1,453 ± 427.9	28,593 ± 6,129	50.9 ± 6.85	2.86 ± 0.63	205.7 ± 20.4
IR700 carboxylate	40	Male	3	0.06 ± 0.00	0.10 ± 0.01	—	—	—
		Female	3	0.06 ± 0.01	0.14 ± 0.03	—	—	—
	80	Male	5	0.14 ± 0.02	0.36 ± 0.14	3.39, 2.73*	126,255, 137,633*	496,718, 673,061*
		Female	5	0.10 ± 0.02	0.24 ± 0.05	—	—	—

Mean ± SD (individual values at n = 2); * n = 2; —, Not calculated

4.3 Distribution

A single dose of cetuximab sarotalocan at 40 or 80 mg/kg was intravenously administered over 2 hours to male and female monkeys to investigate distribution of cetuximab sarotalocan by spectrofluorometry. At (a) Day 3 of administration at 40 mg/kg and (b) Day 15 of administration at 80 mg/kg, fluorescence intensity with the radioactivity concentration higher in the tissue than that in blood (tissue/blood >1) was shown in (a) liver, gallbladder, and axillary lymph node, and (b) inguinal lymph node, mesenteric lymph node, prostate, and axillary lymph node. At Day 3 and 15 of administration, 38.4% and 2.84%, respectively, of the total dose of cetuximab sarotalocan were estimated to remain in the tissues overall.

Cetuximab sarotalocan was distributed in EGFR-expressing tissues as with cetuximab.²⁾

Neither placental nor fetal transfer of cetuximab sarotalocan has been investigated. The applicant explains that cetuximab sarotalocan may cross the placenta and be transferred into the fetus because cetuximab, a component of cetuximab sarotalocan, has been reported to be transferred into the fetus (see “Review Report on Erbitux Injection 100 mg dated May 7, 2008”).

4.4 Metabolism and excretion

The applicant’s explanation:

Metabolism and excretion of cetuximab sarotalocan has not been studied for the following reasons:

- Because cetuximab, a component of cetuximab sarotalocan, is an antibody drug and thus is expected to be eliminated by protein degradation pathway and other pathways, such studies are considered unnecessary as indicated in the “Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals” (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).
- After intravenous administration of cetuximab sarotalocan, serum concentrations of IR700 carboxylate were below the lower limit of quantification values at most of the sampling points, indicating limited transfer of the drug moiety of cetuximab sarotalocan into circulation [see Section 4.2.1].
- The drug moiety of cetuximab sarotalocan is unlikely to be metabolized by drug-metabolizing enzymes in light of its physicochemical properties.³⁾

²⁾ Compared with the control group in which a single dose of cetuximab at 16 mg/kg was intravenously administered over 2 hours.

³⁾ The moiety has a zwitterionic part surrounding a hydrophobic part, rendering its structure highly water soluble.

In addition, the applicant explains that cetuximab sarotalocan may be excreted into milk, because human IgG is excreted into milk (*J Mammary Gland Biol Neoplasia*. 1996;1:243-9 and others), and cetuximab sarotalocan has the constant region of human IgG.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about non-clinical pharmacokinetic findings of cetuximab sarotalocan was acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results of single-dose toxicity studies, genotoxicity studies, and phototoxicity study as toxicity data of cetuximab sarotalocan.

Unless otherwise specified, phosphate buffer was used as vehicle.

5.1 Single-dose toxicity

Single intravenous dose toxicity studies were conducted in rats (IR700 carboxylate administered) and cynomolgus monkeys (cetuximab sarotalocan administered) (Table 10). The exposure (C_{max} and AUC_{inf}) to cetuximab sarotalocan at a no observed adverse effect level (NOAEL) (80 mg/kg/day) in cynomolgus monkeys were 1,624.2 (male) and 1,173.8 (female) $\mu\text{g}/\text{mL}$ for C_{max} and 43,098.3 (male) and 41,092.4 (female) $\mu\text{g}\cdot\text{h}/\text{mL}$ for AUC_{inf} , which were 3.2 and 2.8 times the respective PK parameter values⁴⁾ at a clinical dose.

Table 10. Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose/NOAEL (mg/kg)	Attached document CTD
Male and female rats (Sprague Dawley)	Intravenous	IR700 carboxylate: 0, 10, 30, 100	Death/moribund euthanasia: 100 (2 of 18 males, 2 of 18 females) 100: Decreased physical activity, uncoordinated locomotor activity, high ALT and AST values, Harderian gland necrosis and inflammation, brown adipose tissue degeneration, pulmonary vein inflammation, posterior ocular muscle degeneration and inflammation, adrenal necrosis, and myocardial degeneration and inflammation ≥ 10 : Blue green skin, blue urine Reversibility (2 weeks): reversible ^{a)}	Approximate lethal dose: 100 NOAEL: 30	4.2.3.1.2
Male and female cynomolgus monkeys	Intravenous	Cetuximab sarotalocan: 0, 40, 80 Cetuximab: 16	No noteworthy findings	NOAEL: 80	4.2.3.1.4

a) Regenerating Harderian gland observed

5.2 Repeated-dose toxicity

No repeated-dose toxicity studies of cetuximab sarotalocan have been conducted.

⁴⁾ In Japanese patients who intravenously received a single dose of cetuximab sarotalocan at 640 mg/m², C_{max} and AUC_{inf} were 370 $\mu\text{g}/\text{mL}$ and 14,700 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively.

5.3 Genotoxicity

Genotoxicity of cetuximab sarotalocan was investigated in bacterial reverse mutation assay and human peripheral blood lymphocyte micronucleus assay *in vitro* as well as rat bone marrow micronucleus assay *in vivo* (Table 11). IR700 carboxylate was used in any assay, and the results were negative. Cetuximab sarotalocan was thus considered unlikely to induce genotoxicity *in vivo*.

Table 11. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Photo-irradiation ^{a)}	Concentration (µg/plate or µg/mL) Dose (mg/kg/day)	Result	Attached document CTD
<i>In vitro</i>	Bacterial reverse mutation assay (Ames test)	<i>Salmonella typhimurium</i> : TA98, TA100, TA1535, TA1537 <i>Escherichia coli</i> : WP2 <i>uvrA</i>	S9-	No	0, ^{b)} 100, 250, 500, 1000, 2500, 5000	Negative	4.2.3.3.1.1
			S9+		0, ^{b)} 100, 250, 500, 1000, 2500, 5000	Negative	
			S9-	Yes	0, ^{b)} 2.5, 5.0, 10, 25, 50, 100, 250, 500	Negative	
			S9+		0, ^{b)} 2.5, 5.0, 10, 25, 50, 100, 250, 500	Negative	
	Human peripheral blood lymphocyte micronucleus assay	Human peripheral blood lymphocyte	S9- (4 hours)	No	0, ^{b)} 125, 250, 500	Negative	4.2.3.3.1.2
			S9+ (4 hours)		0, ^{b)} 125, 250, 500	Negative	
			S9- (24 hours)		0, ^{b)} 125, 250, 500	Negative	
			S9- (4 hours)	Yes	0, ^{b)} 125, 250, 500	Negative	
			S9+ (4 hours)		0, ^{b)} 125, 250, 500	Negative	
			S9- (24 hours)		0, ^{b)} 125, 250, 500	Negative	
<i>In vivo</i>	Rat micronucleus assay	Male and female rats (Sprague Dawley) Bone marrow			0, 20, 40, 80 (2 intravenous doses)	Negative	4.2.3.3.2.1

a) LED lighting 5,000 K for 30 minutes (approximately 37,000 lux); b) Calcium/magnesium-free Dulbecco's phosphate buffered saline

5.4 Carcinogenicity

Because cetuximab sarotalocan is an antineoplastic agent intended for treatment of advanced cancer, no carcinogenicity studies have been conducted.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies of cetuximab sarotalocan have been conducted.

Cetuximab, a component of cetuximab sarotalocan, has been reported to induce abortion or embryonic death, and thus cetuximab sarotalocan may also affect the embryo-fetal development. The applicant plans to include in the package insert a precaution statement to the effect that cetuximab sarotalocan may adversely affect the fetus.

5.6 Local tolerance

No local tolerance studies have been conducted. In addition, in a single-dose toxicity study of cetuximab sarotalocan, no noteworthy effect was observed at the administration site.

5.7 Other studies

5.7.1 Phototoxicity

A phototoxicity study in cynomolgus monkeys was conducted to evaluate an effect of cetuximab sarotalocan/laser beam irradiation on normal tissues (Table 12). In this study, a laser beam (50 J/cm²) at 690 nm was applied to the skin 24 hours after a single dose of cetuximab sarotalocan at 40 mg/kg. Although erythema and oedema were observed at the laser beam irradiation site, both were confirmed to be reversible.

Table 12. Phototoxicity study

Test system	Route of administration	Dose (mg/kg)	Major findings	Attached document CTD
Male cynomolgus monkeys	Intravenous	40	Erythema and oedema at the laser beam irradiation site (until 13 days of study). Single cell necrosis and epidermal hyperplasia in epidermis and hair follicle in skin tissue 29 days from the start of the study.	4.2.3.7.7

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and review in the following section, PMDA concluded that the applicant's explanation about toxicity of cetuximab sarotalocan was acceptable.

5.R.1 Repeated-dose toxicity studies

The applicant's explanation about reasons for not conducting repeated-dose toxicity studies:

The repeated-dose toxicity studies of cetuximab sarotalocan were not conducted because cetuximab sarotalocan is not predicted to accumulate in light of its dosing interval and half-life, and the safety in humans was considered predictable from the single-dose toxicity study results.

PMDA's view:

In light of the following points besides the above applicant's explanation, omission of the repeated-dose toxicity studies was acceptable for this application:

- In the single-dose toxicity study in monkeys, no toxicological findings were observed even at up to the limit of injection dose, and no delayed toxicity was found during the observation period up to 28 days post-dose [see Section 5.1].
- In clinical studies of cetuximab sarotalocan, no toxicological findings were observed in patients who received multiple doses of cetuximab sarotalocan [see Section 7.R.3.7].
- The target population of cetuximab sarotalocan in this application is patients with poor-prognosis advanced cancer.

5.R.2 Photo-genotoxicity

In the micronucleus assay in human peripheral blood lymphocyte, no cytotoxicity was observed when exposed to light (LED light). Concerning this finding, PMDA asked the applicant to explain appropriateness of the lighting condition and phototoxicity potential of cetuximab sarotalocan.

The applicant's response:

The main absorption wavelengths of phenol red, contained in the culture medium used in the above micronucleus assay, are 415 and 560 nm, and are different from the maximum absorption wavelength of cetuximab sarotalocan (689 nm), thus excitation light is unlikely to be absorbed by the culture medium. The lighting condition is therefore considered appropriate. In addition, singlet oxygen may contribute to the damage on cell membrane given by cetuximab sarotalocan [see Section 3.1.2], but cetuximab sarotalocan does not penetrate the cell membrane, and thus singlet oxygen generated from cetuximab sarotalocan is unlikely to affect intranuclear DNA. A photo-genotoxicity potential of cetuximab sarotalocan is therefore considered negligible.

PMDA accepted the applicant's explanation.

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

6.1.1 Analytical method

6.1.1.1 Measurement method of cetuximab sarotalocan

Human serum concentrations of cetuximab sarotalocan and IR700 carboxylate were determined by the [REDACTED] method, and their lower limits of quantification were 2.0 and 0.025 µg/mL, respectively.

6.1.1.2 Measurement method of anti-cetuximab sarotalocan antibody and anti-cetuximab sarotalocan neutralizing antibody

Anti-cetuximab sarotalocan antibody in human serum was detected by the ELISA method using solid-phased [REDACTED], [REDACTED] and [REDACTED]-labeled cetuximab sarotalocan as well as [REDACTED]-labeled [REDACTED]. The detection sensitivity was 50.6 ng/mL.

Anti-cetuximab sarotalocan neutralizing antibody in human serum was detected by a fluorescence detection method using human squamous cell carcinoma A431 cell line. The detection sensitivity was 1,249 ng/mL.

6.1.2 Changes on manufacturing processes of the drug substance and drug product in course of development

The manufacturing processes of the drug substance and drug product were changed in a course of development [see Sections 2.1.3.2 and 2.2.3]. In a foreign phase I/IIa study (Study 101) and Japanese phase I study (Study 102), from which data were submitted in this application, cetuximab sarotalocan manufactured by Process [REDACTED] was used.

When the changes were made on the manufacturing processes of the drug substance and drug product, comparability evaluation on quality properties was conducted and has demonstrated comparability between the pre- and post-change drug substances or drug products [see Sections 2.1.3.2 and 2.2.3].

6.2 Clinical pharmacology

PK of cetuximab sarotalocan was investigated in patients with cancer who received cetuximab sarotalocan alone.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2.2, Study 102, March to July 2018)

An open-label, uncontrolled study was conducted to investigate PK of cetuximab sarotalocan in 3 patients with unresectable locally recurrent⁵⁾ head and neck squamous cell carcinoma (3 patients included in the PK analysis). In this study, a single dose of cetuximab sarotalocan was intravenously administered at 640 mg/m² over 2 hours on Day 1 to measure serum concentrations of cetuximab sarotalocan and IR700 carboxylate. In addition, at 20 to 28 hours after administration of cetuximab sarotalocan, a laser beam at 690 nm (irradiation energy density of 50 J/cm² for superficial lesion or 100 J/cm for deep lesion⁶⁾) was applied with a semiconductor laser device.

Table 13 shows PK parameters of cetuximab sarotalocan. Serum concentrations of IR700 carboxylate remained below the lower limit of quantification at all the post-dose sampling points, including one just after administration of cetuximab sarotalocan.⁷⁾

No anti-cetuximab sarotalocan antibody was detected in serum samples from any of the 3 patients who were subjected to the measurement.

Table 13. PK parameters of cetuximab sarotalocan

n	C _{max} (µg/mL)	AUC _{0-26h} (µg•h/mL)	AUC _{last} (µg•h/mL)	t _{1/2} (h)	CL (mL/h/m ²)	V _{ss} (mL/m ²)
3	370 ± 17.2	5,280 ± 529	14,300 ± 1,490	60.5 ± 9.94	43.9 ± 5.26	3,070 ± 223

Mean ± SD

6.2.2 Foreign clinical study

6.2.2.1 Foreign phase I/IIa study (CTD 5.3.3.2.1, Study 101, June 2015 to May 2018)

An open-label, uncontrolled study was conducted to investigate PK and other parameters of cetuximab sarotalocan in 39 patients with unresectable locally recurrent⁸⁾ head and neck squamous cell carcinoma (9 patients in the phase I part and 30 patients⁹⁾ in the phase IIa part included in the PK analysis). In the phase I part of this study, a single dose of cetuximab sarotalocan was intravenously administered at 160, 320, or 640 mg/m² over 2 hours, and in the phase IIa part, up to 4 doses of cetuximab sarotalocan were intravenously administered at 640 mg/m² over 2 hours for each dose. Serum concentrations of cetuximab sarotalocan and IR700 carboxylate were measured. In addition, at 21 to 27 hours after administration of cetuximab sarotalocan, a laser beam at 690 nm (irradiation energy density of 50 J/cm² for superficial lesion or 100 J/cm for deep lesion⁶⁾) was applied with a semiconductor laser device.

Tables 14 and 15 show PK parameters of cetuximab sarotalocan and IR700 carboxylate in the phase I part and phase IIa part. In the dose range studied, the C_{max} and AUC values of cetuximab sarotalocan were almost dose proportional.

Of 33 patients who were subjected to measurement of anti-cetuximab sarotalocan antibody (8 in the phase I part, 25 in the phase IIa part), 2 patients in the phase I part and 1 patient in the phase IIa part

⁵⁾ Patients with locally recurrent cancer who were resistant to radiotherapy (RT) or chemotherapy including platinum antineoplastic agents and had difficulty in receiving standard treatment

⁶⁾ Amount of energy per unit length of fiber

⁷⁾ The concentration just after administration of cetuximab sarotalocan was 0.0342 ± 0.00135 µg/mL.

⁸⁾ Patients with locally recurrent cancer who were resistant to RT or chemotherapy including platinum antineoplastic agents

⁹⁾ In the phase IIa part, 1 patient from the phase I part was included.

were found to have anti-cetuximab sarotalocan antibody in serum after administration of cetuximab sarotalocan. In addition, neutralizing antibody was detected in a serum specimen from 1 patient in the phase IIa part.

Table 14. PK parameters of cetuximab sarotalocan and IR700 carboxylate in phase I part

Dose (mg/m ²)	Analyte	n	C _{max} (µg/mL)	AUC _{0-26h} (µg•h/mL)	AUC _{last} (µg•h/mL)	t _{1/2} (h)	CL (mL/h/m ²)	V _{ss} (mL/m ²)
160* ¹	Cetuximab sarotalocan	3	59.5 ± 5.15	810 ± 51.4	1,580 ± 425	37.8 ± 12.0	89.1 ± 16.4	4,250 ± 493
320	Cetuximab sarotalocan	3	130 ± 15.3	1,790 ± 170	4,070 ± 134	48.6 ± 2.50	73.7 ± 2.13	4,440 ± 432
	IR700 carboxylate	3	0.041 ± 0.007	—	0.105* ²	—	—	—
640	Cetuximab sarotalocan	3	271 ± 56.7	3,910 ± 1,090	11,500 ± 6,980	77.5 ± 34.8	56.7 ± 23.9	4,840 ± 958
	IR700 carboxylate	3	0.063 ± 0.011	—	0.947 ± 1.27	—	—	—

Mean ± SD; —, Not calculated; *¹ Concentrations of IR700 carboxylate in patients treated with cetuximab sarotalocan at 160 mg/m² were below the lower limit of quantification at any sampling point, precluding calculation of PK parameters; *² n = 1

Table 15. PK parameters of cetuximab sarotalocan and IR700 carboxylate in phase IIa part

Cycle	Analyte	n	C _{max} (µg/mL)	AUC _{0-26h} (µg•h/mL)	AUC _{last} (µg•h/mL)	t _{1/2} (h)	CL (mL/h/m ²)	V _{ss} (mL/m ²)
1	Cetuximab sarotalocan	30	296 ± 73.0	3,900 ± 1,090* ¹	9,300 ± 3,920* ²	56.0 ± 19.5* ¹	71.2 ± 47.8* ¹	4,370 ± 1,370* ¹
	IR700 carboxylate	30	0.059 ± 0.019	—	0.283 ± 0.328* ³	—	—	—
2	Cetuximab sarotalocan	9	300 ± 63.2	4,090 ± 1,270* ⁴	9,190 ± 4,550* ⁴	51.8 ± 16.9* ⁵	65.1 ± 25.8* ⁵	4,200 ± 1,690* ⁵
	IR700 carboxylate	9	0.049 ± 0.019	—	0.215, 1.02* ⁶	—	—	—
3	Cetuximab sarotalocan	6	334 ± 65.7	4,480 ± 665	7,180 ± 3,270	35.1 ± 19.8	71.7 ± 15.8	3,020 ± 1,120
	IR700 carboxylate	5	0.041 ± 0.013	—	—	—	—	—
4	Cetuximab sarotalocan	4	283 ± 52.2	4,920, 4,930* ⁶	6,050 ± 6,390	37.4, 72.6* ⁶	41.2, 57.2* ⁶	2,830, 3,820* ⁶
	IR700 carboxylate	4	0.051 ± 0.019	—	0.140, 0.189* ⁶	—	—	—

Mean ± SD (individual values at n = 2); —, Not calculated; *¹ n = 26; *² n = 28; *³ n = 11; *⁴ n = 8; *⁵ n = 7; *⁶ n = 2

6.2.3 Relationships of exposure with efficacy and safety

On the basis of the results from Studies 101 and 102, relationships of exposure¹⁰⁾ to cetuximab sarotalocan (C_{max} and AUC_{0-∞}) with the efficacy and safety were investigated.

6.2.3.1 Relationships of exposure with efficacy

Relationships of C_{max} and AUC_{0-∞} of cetuximab sarotalocan with response rates were investigated. No clear relationships of C_{max} and AUC_{0-∞} of cetuximab sarotalocan with response rates were observed.

6.2.3.2 Relationships of exposure with safety

Relationships of C_{max} and AUC_{0-∞} of cetuximab sarotalocan with serious adverse events, Grade ≥3 adverse events, and noteworthy adverse events¹¹⁾ were investigated. No clear relationships of C_{max} and AUC_{0-∞} of cetuximab sarotalocan with the occurrences of the above adverse events were observed.

¹⁰⁾ Before the evaluation, patients treated with cetuximab sarotalocan were divided into 4 groups according to quartiles of exposure to cetuximab sarotalocan in terms of (a) C_{max} (µg/mL) and (b) AUC_{0-∞} (µg•h/mL) as follows: (a) ≥54.8 and ≤220; >220 and ≤275; >275 and ≤332; >332 and ≤489; and (b) ≥1,586.4 and ≤7,191.7; >7,191.7 and ≤10,295.2; >10,295.2 and ≤12,854.6; >12,854.6 and ≤22,031.5.

¹¹⁾ Defined as haemorrhage, skin reaction, photosensitivity, inflammation, pain localised, and oedema

6.2.4 Effects of renal and hepatic impairment on PK of cetuximab sarotalocan

No clinical studies to investigate PK of cetuximab sarotalocan in patients with renal or hepatic impairment have been conducted.

The applicant's explanation:

Renal or hepatic impairment is considered unlikely to affect PK of cetuximab sarotalocan in light of the following points:

- The antibody moiety of cetuximab sarotalocan is supposed to be eliminated by binding to the target antigen and protein degradation pathway, and thus renal or hepatic impairment is considered unlikely to affect exposure to cetuximab sarotalocan.
- For the drug moiety of cetuximab sarotalocan, its release from the conjugate is limited,¹²⁾ and thus renal or hepatic impairment is considered unlikely to affect exposure to the drug moiety.

6.2.5 Difference in PK of cetuximab sarotalocan between Japanese and non-Japanese patients

The applicant's explanation:

In light of the following points, no clear differences have been observed in PK of cetuximab sarotalocan or IR700 carboxylate between Japanese and non-Japanese patients:

- No clear differences have been observed in PK parameters of cetuximab sarotalocan between Japanese and non-Japanese patients [see Sections 6.2.1.1 and 6.2.2.1].
- In both Japanese and non-Japanese patients, serum concentrations of IR700 carboxylate reached the maxima (C_{max}) of a similar level just after the end of administration of cetuximab sarotalocan and then fell below the lower limit of quantification.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about clinical pharmacology findings of cetuximab sarotalocan was acceptable except for matters reviewed in the following section.

6.R.1 Effects of anti-cetuximab sarotalocan antibody on PK of cetuximab sarotalocan

Development of anti-cetuximab sarotalocan antibody was investigated in all the clinical studies from which data were submitted in this application. Of 36 patients eligible for evaluation¹³⁾ of anti-cetuximab sarotalocan antibody, 4 patients¹⁴⁾ (11.1%) were found to have anti-cetuximab sarotalocan antibody.

The applicant's explanation:

Anti-cetuximab sarotalocan antibody is unlikely to affect PK of cetuximab sarotalocan because serum concentrations of cetuximab sarotalocan in 4 patients positive for anti-cetuximab sarotalocan antibody did not tend to be different from those in patients negative for the antibody in Studies 101 and 102.

¹²⁾ In a Japanese phase I study (Study 102), the C_{max} value of IR700 carboxylate was approximately 0.7% of that of cetuximab sarotalocan on a molar basis in patients intravenously treated with a single dose of cetuximab sarotalocan at 640 mg/m².

¹³⁾ Serum concentrations of cetuximab sarotalocan were below the lower limit of quantification in most of the specimens at a point closest to the measurement of anti-cetuximab sarotalocan antibody.

¹⁴⁾ Including 1 patient in whom anti-cetuximab sarotalocan antibody was detected only before the first dose of cetuximab sarotalocan (baseline) in a foreign phase I/IIa study (Study 101)

PMDA's view:

It is difficult to reach a clear conclusion about the effect of anti-cetuximab sarotalocan antibody on PK of cetuximab sarotalocan because of the limited number of patients positive for the antibody. The applicant should continue collecting information on the concerned effect and, if a new finding becomes available, provide the information to healthcare professionals in an appropriate manner.

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 data from a total of 2 clinical studies, 1 Japanese phase I study and 1 foreign phase I/IIa study, listed in Table 16.

Table 16. List of clinical studies for efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	Number of enrollments (n)	Dosing regimen	Primary endpoint
Evaluation	Japan	Study 102	I	Patients with unresectable locally recurrent head and neck squamous cell carcinoma	5	A single dose of cetuximab sarotalocan was intravenously administered at 640 mg/m ² over 2 hours, and at 20-28 hours post-dose, a laser beam ^{*2} was applied with a semiconductor laser device. ^{*1}	Efficacy Safety PK
	Foreign	Study 101	I/IIa	Patients with unresectable locally recurrent head and neck squamous cell carcinoma	(a) Phase I part, 9 (b) Phase IIa part, ^{*3} 31	(a) A single dose of cetuximab sarotalocan was intravenously administered at 160, 320, or 640 mg/m ² over 2 hours, and at 21-27 hours post-dose, a laser beam ^{*2} was applied with a semiconductor laser device. ^{*4} (b) Cetuximab sarotalocan was intravenously administered at 640 mg/m ² over 2 hours, and at 21-27 hours post-dose, a laser beam ^{*2} was applied ^{*5} with a semiconductor laser device. ^{*4}	Efficacy Safety PK

^{*1} PIT690.4-2500 (Rakuten Medical) was used; ^{*2} Irradiation energy density of 50 J/cm² for superficial lesion and 100 J/cm for deep lesion (amount of energy per unit length of fiber); ^{*3} The phase IIa part also included 1 patient from the phase I part; ^{*4} ML7710-690-ASP (Modulight) was used; ^{*5} Up to 4 cycles of cetuximab sarotalocan/laser beam irradiation at intervals of 4-8 weeks were allowed.

Outline of each clinical study is as provided below. The main adverse events other than deaths observed in each clinical study are presented in Section "7.2 Adverse events observed in clinical studies," and PK-related data are presented 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 5.3.3.2-2, Study 102, March to July 2018)

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent⁵⁾ head and neck squamous cell carcinoma (target sample size, 3-6 subjects) at a single study site in Japan.

A single dose of cetuximab sarotalocan was intravenously administered at 640 mg/m² over 2 hours.¹⁵⁾ In addition, at 20 to 28 hours after administration of cetuximab sarotalocan, a laser beam at 690 nm (irradiation energy density of 50 J/cm² for superficial lesion or 100 J/cm for deep lesion⁶⁾) was applied with a semiconductor laser device.

Of 5 patients enrolled in this study, 3 patients who received cetuximab sarotalocan were included in the efficacy analysis. The same analysis population was used for the safety analysis.

The dose-limiting toxicity (DLT) evaluation period was until Day 7 of administration of cetuximab sarotalocan, but no DLT occurred.

Table 17 shows results on the response rate centrally assessed according to revised Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1¹⁶⁾ (data cut-off on November 6, 2018).

Table 17. Best overall response and response rate (revised RECIST ver.1.1, efficacy analysis population, central assessment, data cut-off November 6, 2018)

Best overall response	Number of patients (%)
	n = 3
CR	0
PR	2 (66.7)
SD	0
PD	1 (33.3)
NE	0
Response (CR + PR) (response rate [95% CI*] [%])	2 (66.7 [9.4, 99.2])

* Clopper-Pearson method

No deaths occurred during administration or within 28 days after the end of the administration of cetuximab sarotalocan.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase I/IIa study (CTD 5.3.5.2-1, Study 101, June 2015 to May 2018)

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent⁸⁾ head and neck squamous cell carcinoma (target sample size; 12-24 patients in phase I part, 30 patients in phase IIa part) at 7 study sites outside of Japan.

Cetuximab sarotalocan was intravenously administered at 160, 320, or 640 mg/m² in the phase I part and at 640 mg/m² in the phase IIa part over 2 hours for each dose.¹⁵⁾ In addition, at 21 to 27 hours after administration of cetuximab sarotalocan, a laser beam at 690 nm (irradiation energy density of 50 J/cm² for superficial lesion or 100 J/cm for deep lesion⁶⁾) was applied with a semiconductor laser device. Of patients included in the phase IIa part, patients who did not achieve complete response (CR) after the first cycle of cetuximab sarotalocan/laser beam irradiation were allowed to receive up to 4 cycles at intervals of 4 to 8 weeks.

¹⁵⁾ To prevent infusion reaction, dexamethasone sodium phosphate at 3.3 mg and *d*-chlorpheniramine maleate at 5 mg were intravenously administered, and at 15 to 30 minutes after the end of the prophylactic administration, cetuximab at 100 mg was intravenously administered over ≥30 minutes as a challenge dose. When no Grade ≥3 infusion reaction was observed during administration of cetuximab, cetuximab sarotalocan was administered at 30 to 90 minutes after the end of the administration of cetuximab.

¹⁶⁾ Because cetuximab sarotalocan/laser beam irradiation is intended for local treatment, a lesion subjected to laser beam irradiation was defined as the target lesion and a lesion not subjected to the application as the non-target lesion.

Of 40 patients enrolled in this study (9 in the phase I part, 31 in the phase IIa part⁹⁾), 39 patients who received cetuximab sarotalocan (9 in the phase I part, 30 in the phase IIa part⁹⁾) were included in the efficacy analysis. The same analysis population was used for the safety analysis.

In the phase I part, the DLT evaluation period was until Day 7 of administration of cetuximab sarotalocan. No DLT occurred, and the recommended dose of cetuximab sarotalocan was determined to be 640 mg/m².

Table 18 shows results on the response rate centrally assessed according to revised RECIST ver.1.1¹⁵⁾ in the phase IIa part of this study (data cut-off on March 12, 2019).

**Table 18. Best overall response and response rate
(revised RECIST ver.1.1, phase IIa part, efficacy analysis population, central assessment,
data cut-off March 12, 2019)**

Best overall response	Number of patients (%)
	n = 30
CR	4 (13.3)
PR	9 (30.0)
SD	11 (36.7)
PD	5 (16.7)
NE	1 (3.3)
Response (CR + PR) (response rate [95% CI*] [%])	13 (43.3 [25.5, 62.6])

* Clopper-Pearson method

Deaths occurred in 3 of 30 patients (10.0%) in the phase IIa part during administration or within 28 days after the end of the administration of cetuximab sarotalocan. Causes of the deaths were pneumonia,¹⁷⁾ tumour haemorrhage,¹⁸⁾ and arterial haemorrhage¹⁹⁾ in 1 patient each, and a causal relationship to cetuximab sarotalocan/laser beam irradiation was ruled out for any of these events.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA decided that the most important data submitted for the evaluation of the efficacy and safety of cetuximab sarotalocan/laser beam irradiation was those of a foreign phase I/IIa study (Study 101) in patients with unresectable locally recurrent head and neck squamous cell carcinoma previously treated with chemotherapy including platinum antineoplastic agents conducted to evaluate the efficacy and safety of cetuximab sarotalocan/laser beam irradiation. The agency therefore focused on data from the phase IIa part of this study in the review of cetuximab sarotalocan/laser beam irradiation

In addition, PMDA decided to review the efficacy and safety of cetuximab sarotalocan/laser beam irradiation in Japanese patients mainly on data from a Japanese phase I study (Study 102), which was

¹⁷⁾ A 71-year old man. The patient experienced deep vein thrombosis (Grade 2) (causal relationship to cetuximab sarotalocan/laser beam irradiation was denied) at Day 14 after the fourth cycle of cetuximab sarotalocan/laser beam irradiation and received an anticoagulant agent. At Day 29, he complained of abdominal pain and received diagnoses of intra-abdominal haemorrhage (Grade 3) and pneumonia. He received antimicrobial agents and oxygen, transferred to a hospice at Day 38, and died at Day 41. A causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for both intra-abdominal haemorrhage and pneumonia.

¹⁸⁾ A 51-year old man. The patient experienced haemorrhage from a lesion of head and neck squamous cell carcinoma that was not subjected to cetuximab sarotalocan/laser beam irradiation at Day 18 after the second cycle and died at Day 19.

¹⁹⁾ A 51-year old woman. The patient experienced myocardial infarction (Grade 4) and sepsis (Grade 4) at Day 24 after the third cycle of cetuximab sarotalocan/laser beam, recovered from these events at Day 33, and was discharged (a causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for both events). Arterial haemorrhage occurred at home on the day of discharge, resulting in death.

conducted in the patients with head and neck squamous cell carcinoma as those described above to evaluate the efficacy and safety of cetuximab sarotalocan/laser beam irradiation.

7.R.2 Clinical positioning and efficacy

On the basis of the following review, PMDA has concluded that cetuximab sarotalocan/laser beam irradiation has a certain level of efficacy in patients with unresectable locally recurrent head and neck cancer.

7.R.2.1 Clinical positioning

Description on cetuximab sarotalocan/laser beam irradiation was not found in the 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 recurrent head and neck cancer and clinical positioning of cetuximab sarotalocan/laser beam irradiation in the concerned algorithm:

The standard treatments for patients with unresectable locally advanced head and neck cancer are chemoradiotherapy (CRT) including platinum antineoplastic agents and radiotherapy (RT). For patients who experience local recurrence or metastasis after the above treatment, chemotherapy including nivolumab (genetical recombination) (nivolumab) and cetuximab is provided as the standard treatment.

The treatment for unresectable locally advanced or recurrent head and neck cancer is provided with expectation of survival benefit, but the local lesion may impair functions such as vocalization, swallowing, chewing, and breathing, and thus control of local lesions for functional preservation has a clinical significance (*New Clinical Oncology*. fifth revised edition. Nankodo Co., Ltd., 2018). The standard treatment with nivolumab, however, has limited effectiveness on local lesions, as shown in the ONO-4538-11/CA209141 study (the CheckMate 141 study)²⁰⁾ of nivolumab, in which the response rate [95% confidence interval (CI)] (%) assessed by investigator according to RECIST ver.1.1 was 13.3 [9.3, 18.3] (*N Engl J Med*. 2016;375:1856-67). Re-irradiation has a risk of serious adverse drug reactions in patients with locally recurrent head and neck cancer previously treated with CRT or RT (*Am J Clin Oncol*. 2008;31:393-8) and thus has not been established as the standard treatment.

In light of the above situations, cetuximab sarotalocan/laser beam irradiation is considered to be positioned as one of local treatment options for patients with unresectable locally advanced or recurrent head and neck cancer based on the following reasons: (a) cetuximab sarotalocan/laser beam irradiation is a local treatment procedure that is expected to damage tumor cells by exciting cetuximab sarotalocan bound to EGFR expressed on tumor cell membrane through a laser beam irradiation at 690 nm with a semiconductor laser device, to have a limited effect on normal tissues around the tumor, and to preserve functions such as vocalization, swallowing, chewing, and breathing by controlling the local lesions; and (b) results on the response rate in the phase IIa part of Study 101 [see Section 7.1.2.1].

²⁰⁾ A global phase III study that was conducted in patients with recurrent or metastasis of head and neck squamous cell carcinoma with the primary site of the oral cavity, oropharynx/hypopharynx, or larynx in whom disease progression or recurrence occurred within 6 months after the end of chemotherapy including platinum antineoplastic agents (including definitive or postoperative chemoradiotherapy) to compare the efficacy and safety between nivolumab and the investigator's choice (IC) (cetuximab, methotrexate [MTX], or docetaxel hydrate [DTX]) (*N Engl J Med* 2016;375:1856-67)

In Japan, boron neutron capture therapy (BNCT) using borofalan (^{10}B) has been approved as a local treatment procedure indicated for patients with unresectable locally advanced or recurrent head and neck cancer, but results from a clinical study comparing the efficacy and safety between the concerned BNCT and cetuximab sarotalocan/laser beam irradiation have not been available, and which procedure should be chosen for what condition remains unclear. A choice may be made according to the patient's condition.

PMDA's view:

PMDA largely accepted the applicant's explanation. Clinical positioning of cetuximab sarotalocan will be further clarified by results from the currently ongoing clinical study below, and thus results from the concerned study, when available, should be provided to healthcare professionals in an appropriate manner.

- An open-label, randomized, global phase III study (RM-1929-301 study [Study 301]) that was conducted in patients with unresectable locally recurrent head and neck squamous cell carcinoma treated with ≥ 2 prior therapies (target sample size, 275 patients) to compare the efficacy (primary endpoints, progression free survival [PFS] and overall survival [OS]) and safety between cetuximab sarotalocan/laser beam irradiation and investigator's choice (IC) (cetuximab, methotrexate [MTX], or docetaxel hydrate [DTX])

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about efficacy endpoint and evaluation results in the phase IIa part of Study 101:

Patients with unresectable locally recurrent head and neck cancer, if they respond to the procedure, will be able to preserve functions such as vocalization, swallowing, chewing, and breathing and thereby to improve quality of life (QOL) (*Cancer*. 2017;123:4583-93). The response in the concerned patients is therefore considered clinically meaningful. The efficacy endpoint in the phase IIa part of Study 101 was specified as the response rate.

For the efficacy analysis population in the phase IIa part of Study 101, the efficacy endpoints were (a) the response rate [95% CI] (%) centrally assessed according to revised RECIST ver.1.1,¹⁶⁾ and (b) the response rate [95% CI] (%) assessed by the investigator according to RECIST ver.1.1; and response rates were (a) 43.3 [25.5, 62.6] [see Section 7.1.1.1] and (b) 36.7 [19.9, 56.1], which exceeded the response rate of nivolumab in the CheckMate 141 study²⁰⁾ [see Section 7.R.2.1]. Therefore, cetuximab sarotalocan/laser beam irradiation is expected to be effective in the target patient population in the phase IIa part of Study 101.

Figure 2 shows the best percentage change in tumor size (target lesion) centrally assessed according to revised RECIST ver.1.1¹⁶⁾ in the phase IIa part of Study 101. In addition, the median duration of response²¹⁾ [95% CI] (months) was 12.2 [non-estimable, non-estimable].²²⁾

²¹⁾ It is defined as a period from the first response (CR or partial response [PR]) to progressive disease (PD) or death, whichever comes earlier, in patients with definitive CR or PR. In the case where neither PD nor death occurs or where a new therapy is initiated, the evaluation was censored at the last imaging point.

²²⁾ The duration of response ranged from 2.1 to 12.2 months.

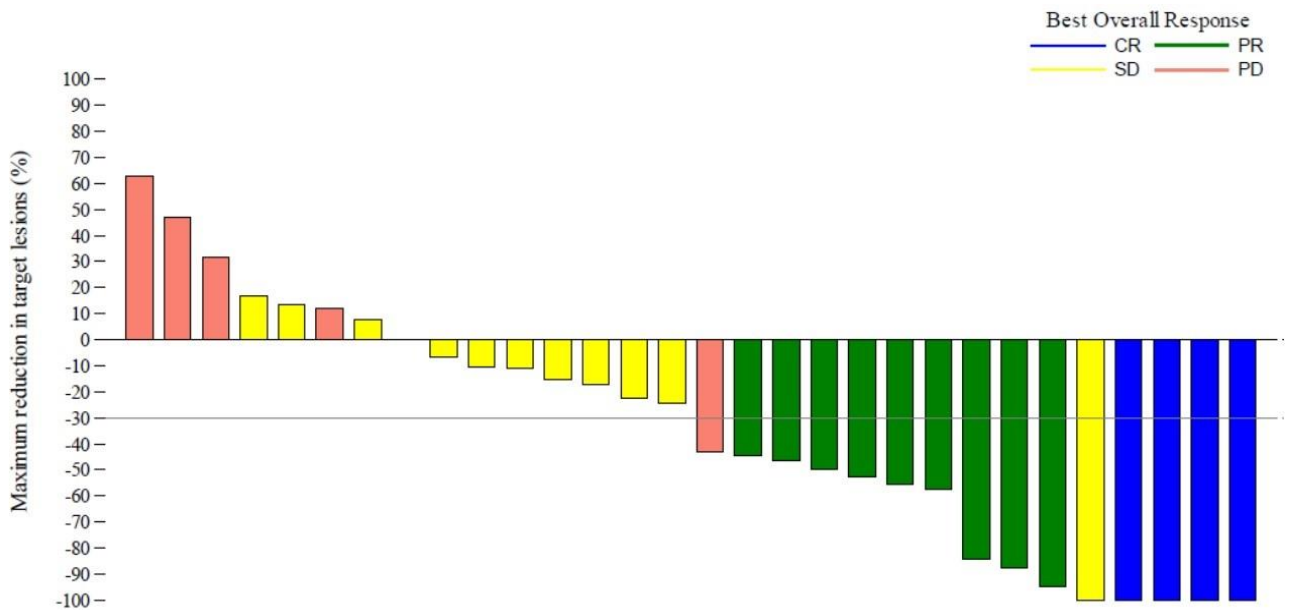


Figure 2. Best percentage change in tumor size (target lesion) (revised RECIST ver.1.1, phase IIa part of Study 101, efficacy analysis population, central assessment)

The applicant’s explanation about the efficacy of cetuximab sarotalocan/laser beam irradiation in Japanese patients:

In Study 102, of Japanese patients with unresectable locally recurrent head and neck squamous cell carcinoma, 2 of 3 patients (66.7%) responded to the procedure [see Section 7.1.1.1].

Although the number of Japanese patients included in the study is limited, cetuximab sarotalocan/laser beam irradiation is also expected to be effective in Japanese patients with unresectable locally recurrent head and neck squamous cell carcinoma in light of the following points:

- No clear differences have been observed in PK of cetuximab sarotalocan between Japanese and non-Japanese patients [see Section 6.2.5].
- No clear differences have been noted in diagnosis or the treatment algorithm of unresectable locally recurrent head and neck cancer between Japan and the other countries.

PMDA’s view:

Because Study 101 was not designed to examine a hypothesis established for the efficacy, it has limitations to evaluate the efficacy of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck squamous cell carcinoma based on results from the concerned study. On the basis of the results from the review in Section “7.R.2.1 Clinical positioning” and in light of the following points, however, cetuximab sarotalocan/laser beam irradiation has a certain level of efficacy in patients with unresectable locally recurrent head and neck squamous cell carcinoma including Japanese patients:

- Local lesions in patients with unresectable locally recurrent head and neck cancer may cause pathological conditions remarkably compromising patients’ QOL, such as dysphagia, malnutrition, airway narrowing, aspiration, and fistula formation, and local control of the lesions has a certain clinical significance.
- In Study 101, certain response to cetuximab sarotalocan/laser beam irradiation was observed.

- In Study 102, response was observed in Japanese patients with unresectable locally recurrent head and neck squamous cell carcinoma as well.

7.R.3 Safety (for adverse events, see Section “7.2 Adverse events observed in clinical studies”)

On the basis of the following review, PMDA considers that adverse events requiring special attentions in treatment with cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck cancer are haemorrhage, swelling, infusion reaction, photosensitivity, and skin reaction (except for photosensitivity). Caution should be exercised against these adverse events in using cetuximab sarotalocan/laser beam irradiation.

In addition, although attention should be exercised against the above adverse events when cetuximab sarotalocan/laser beam irradiation is performed, Cetuximab sarotalocan/laser beam irradiation is tolerable provided that physicians with sufficient knowledge and experience in cancer chemotherapy and photodynamic therapy take appropriate measures such as monitoring and controlling the adverse events.

7.R.3.1 Safety profile

The applicant’s explanation about the safety profile of cetuximab sarotalocan/laser beam irradiation based on the safety information in the phase IIa part of Study 101 and Study 102:

Table 19 shows the outline of safety in the phase IIa part of Study 101 and Study 102.

Table 19. Outline of safety (phase IIa part of Study 101 and Study 102)

	Number of patients (%)	
	Study 101	Study 102
	Phase IIa part n = 30	n = 3
All adverse events	30 (100)	3 (100)
Grade ≥ 3 adverse events	19 (65.3)	1 (33.3)
Adverse events leading to death	3 (10.0)	0
Serious adverse events	13 (43.3)	0
Adverse events leading to discontinuation of cetuximab sarotalocan/ laser beam irradiation	5 (16.7)	0

In the phase IIa part of Study 101, all-Grade adverse events with an incidence of $\geq 20\%$ were fatigue in 10 patients (33.3%), dysphagia in 7 patients (23.3%), and oedema peripheral, constipation, and erythema in 6 patients each (20.0%). Grade ≥ 3 adverse events reported by ≥ 2 patients were anaemia in 3 patients (10.0%), and application site pain, localised oedema, dysphagia, oral pain, hyponatraemia, pneumonia, tumour pain, and tumour haemorrhage in 2 patients each (6.7%). Reported serious adverse events were pneumonia in 3 patients (10.0%), tumour haemorrhage in 2 patients (6.7%), and localised infection, sepsis, tumour pain, oral pain, abdominal pain, oesophagitis, pneumonia aspiration, obstructive airways disorder, pneumothorax, hypoglycaemia, arterial haemorrhage, deep vein thrombosis, internal haemorrhage, anaemia, myocardial infarction, international normalised ratio increased, and urinary tract obstruction in 1 patient each (3.3%). A causal relationship to cetuximab sarotalocan/laser beam

irradiation could not be ruled out for tumour pain,²³⁾ oral pain,²⁴⁾ and obstructive airways disorder²⁵⁾ in 1 patient each. Reported adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation were peripheral swelling, blood creatinine increased, tumour haemorrhage, rash, and arterial haemorrhage in 1 patient each (3.3%).

All-Grade adverse events reported in Study 102 were application site pain, application site oedema, face oedema, localised oedema, blood pressure increased, gamma glutamyl transpeptidase (GGT) increased, white blood cell count decreased, anaemia, glossitis, hepatic function abnormal, and rash generalized in 1 patient each (33.3%). A reported Grade ≥ 3 adverse event was application site pain in 1 patient (33.3%). Neither serious adverse events nor adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred.

Adverse events reported only by Japanese patients were blood pressure increased, GGT increased, white blood cell count decreased, glossitis, hepatic function abnormal, and rash generalized in 1 patient each, and all of these were at Grade ≤ 2 .

PMDA's view:

When cetuximab sarotalocan/laser beam irradiation is performed, attention should be paid to the adverse events frequently reported in phase IIa part of Study 101 and Study 102 as well as serious adverse events and Grade ≥ 3 adverse events reported in the 2 studies. Information on these events should be appropriately provided to healthcare professionals through the package insert. In addition, because safety information on cetuximab sarotalocan/laser beam irradiation in patients with head and neck cancer is very limited, the applicant should continue collecting the post-marketing information and, if new information becomes available, provide the information to healthcare professionals immediately. Although the number of Japanese patients included in Study 102 is limited, cetuximab sarotalocan/laser beam irradiation is also tolerable in Japanese patients provided that appropriate actions such as discontinuation of cetuximab sarotalocan/laser beam irradiation are taken, in light of the following points:

- Neither adverse events leading to death nor serious adverse events occurred in Japanese patients.
- All the adverse events reported only by Japanese patients were at Grade ≤ 2 .

In the following sections, PMDA reviewed the safety results from the phase IIa part of Study 101 and Study 102 with the focus on the adverse events leading to death, serious adverse events for which a causal relationship to cetuximab sarotalocan/laser beam irradiation could not be ruled out, and adverse events requiring attention for cetuximab, a component of cetuximab sarotalocan.

²³⁾ A 71-year old woman. The patient experienced increased tumour pain and pain burning in the neck and pharynx in addition to the laser application site of the tongue on Day 5 of the second cycle of cetuximab sarotalocan/laser beam irradiation and was hospitalized on Day 8. The tongue, the laser application site, was swollen, and pain made swallowing and conversation through a tracheostomy tube difficult. A nasogastric tube was catheterized to administer an opioid preparation. The tumour pain was successfully controlled, and she was discharged on Day 12. The concerned event was judged to have resolved.

²⁴⁾ A 51-year old man. The patient already had oral pain (Grade 2) when enrolled in the study. The oral pain was increased (Grade 3) on Day 13 of the first cycle of cetuximab sarotalocan/laser beam irradiation, and an opioid preparation was administered. On Day 30, the concerned event was judged to have resolved.

²⁵⁾ A 51-year old man. The patient experienced inspiratory stridor and retractive breathing owing to upper airway obstruction during tracheal extubation after the second cycle of cetuximab sarotalocan/laser beam irradiation. Emergent tracheostomy was performed, but oxygen saturation was reduced, and chest radiography showed bilateral pneumothorax complication. A chest drainage catheter was placed. The obstructive airways disorder was considered attributable to upper airway oedema associated with cetuximab sarotalocan/laser beam irradiation and was determined to have resolved on Day 6.

7.R.3.2 Haemorrhage

The applicant's explanation about haemorrhage associated with cetuximab sarotalocan/laser beam irradiation:

Adverse events related to haemorrhage were tabulated based on event terms classified under the preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) of "arterial haemorrhage," "epistaxis," "haemorrhage," "internal haemorrhage," "laryngeal haemorrhage," "mouth haemorrhage," "post procedural haemorrhage," "tumour haemorrhage," and "wound haemorrhage." In Study 102, no events of haemorrhage occurred.

In the phase IIa part of Study 101, all-Grade haemorrhage occurred in 8 of 30 patients (26.7%; tumour haemorrhage in 3 patients; and arterial haemorrhage, haemorrhage, internal haemorrhage, post procedural haemorrhage, wound haemorrhage, epistaxis, laryngeal haemorrhage, and mouth haemorrhage in 1 patient each [some patients had multiple events]). Grade ≥ 3 haemorrhage occurred in 4 of 30 patients (13.3%; tumour haemorrhage in 2 patients; and arterial haemorrhage and internal haemorrhage in 1 patient each). Fatal haemorrhage occurred in 2 of 30 patients (6.7%; tumour haemorrhage¹⁸⁾ and arterial haemorrhage¹⁹⁾ in 1 patient each), but a causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for both events. Serious haemorrhage occurred in 4 of 30 patients (12.2%; tumour haemorrhage in 2 patients; and arterial haemorrhage and internal haemorrhage in 1 patient each), but a causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for all the events. Haemorrhage leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred in 2 of 30 patients (6.7%; tumour haemorrhage and arterial haemorrhage in 1 patient each).

In the phase IIa part of Study 101, the median time to first onset of haemorrhage (range)²⁶⁾ was 19 days (1-34 days).

Table 20 shows details of patients who experienced serious haemorrhage associated with cetuximab sarotalocan/laser beam irradiation in Study 101.

Table 20. List of patients with serious haemorrhage

Study	Age	Sex	PT (MedDRA ver.21.0)	Grade	Cycle No. at onset	Time to onset* ¹ (Day)	Duration (days)	Causal relationship	Outcome
Study 101 Phase I part	5	Male	Tumour haemorrhage* ²	4	1	5	8	Yes	Recovered
	5	Male	Tumour haemorrhage	5	2	21	1	No	Death
Study 101 Phase IIa part	6	Male	Tumour haemorrhage	3	2	1* ³	6	No	Recovered
	5	Female	Arterial haemorrhage	5	3	34	1	No	Death
	8	Male	Internal haemorrhage	3	4	30	13	No	Unknown

*¹ Time to onset in each cycle

*² The patient experienced tumour haemorrhage on Day 5 of administration of cetuximab sarotalocan and was admitted to the emergency room where massive upper respiratory tract haemorrhage was found. Emergent tracheostomy was performed followed by embolization of pseudoaneurysm in the external carotid artery on the facial left side. Then, no re-haemorrhage occurred, and he was discharged on Day 12. The concerned event was determined to have resolved;

*³ Tumour haemorrhage occurred on Day 2 of administration of cetuximab sarotalocan, and no laser beam irradiation was performed.

²⁶⁾ For patients who received multiple cycles of cetuximab sarotalocan/laser beam irradiation, the time to first onset in each cycle.

PMDA asked the applicant to explain the safety of cetuximab sarotalocan/laser beam irradiation in patients with tumor invasion in the carotid artery.

The applicant's response:

Attention should be paid when cetuximab sarotalocan/laser beam irradiation is performed on the concerned patient because (a) cetuximab sarotalocan/laser beam irradiation may result in tumor necrosis, potentially leading to haemorrhage; and (b) a certain percentage of patients experienced haemorrhage in Study 101. Cetuximab sarotalocan/laser beam irradiation is therefore planned to be contraindicated in patients with tumor invasion in the carotid artery who have not undergone vascular embolization, stent placement, or surgical ligation on the affected blood vessel.

PMDA's view:

In clinical studies from which data were submitted, serious haemorrhage for which a causal relationship to cetuximab sarotalocan/laser beam irradiation could not be ruled out occurred, and attention should be paid to haemorrhage when cetuximab sarotalocan/laser beam irradiation is performed. Cautions about the incidence of haemorrhage should be appropriately presented to healthcare professionals by including data from the clinical studies in the package insert.

In addition, Studies 101 and 102 excluded patients with tumor invasion in the carotid artery, and in patients receiving cetuximab sarotalocan/laser beam irradiation, fatal haemorrhage such as arterial haemorrhage occurred. Taking account of the above, cetuximab sarotalocan/laser beam irradiation should be contraindicated in patients with tumor invasion in the carotid artery, and cautions should be appropriately presented to healthcare professionals by including in the package insert a statement to the effect that carotid arterial haemorrhage may occur if such patients receive cetuximab sarotalocan/laser beam irradiation.

7.R.3.3 Swelling

The applicant's explanation about swelling associated with cetuximab sarotalocan/laser beam irradiation:

Adverse events related to swelling were tabulated according to MedDRA PTs of "application site oedema," "application site swelling," "face oedema," "laryngeal oedema," "lip swelling," "localised oedema," "orbital oedema," "periorbital oedema," "skin oedema," "swelling," "swollen tongue," and "tongue oedema."

Table 21 shows the incidences of swelling in the phase IIa part of Study 101 and Study 102.

Table 21. Incidences of swelling reported by ≥ 2 patients in either study (phase IIa part of Study 101 and Study 102)

PT (MedDRA ver.21.0)	Number of patients (%)			
	Study 101 (phase IIa part) n = 30		Study 102 n = 3	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Swelling	18 (60.0)	4 (13.3)	3 (100)	0
Face oedema	5 (16.7)	1 (3.3)	1 (33.3)	0
Swelling	4 (13.3)	0	0	0
Tongue oedema	4 (13.3)	0	0	0
Localised oedema	3 (10.0)	2 (6.7)	1 (33.3)	0
Application site oedema	2 (6.7)	0	1 (33.3)	0
Swollen tongue	2 (6.7)	0	0	0
Laryngeal oedema	2 (6.7)	0	0	0

In the phase IIa part of Study 101 and Study 102, no fatal or serious swelling, or swelling leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred.

In the phase IIa part of Study 101 and Study 102, the median time to first onset of swelling (range)²⁶⁾ was 2.5 days (1-33 days) and 2 days (2-4 days), respectively.

PMDA's view:

In clinical studies from which data were submitted, obstructive airways disorder attributable to oedema associated with cetuximab sarotalocan/laser beam irradiation occurred,²⁵⁾ and attention should be paid to laryngeal oedema owing to a risk of airway narrowing when cetuximab sarotalocan/laser beam irradiation is performed. Information about the incidences of laryngeal oedema in clinical studies should be appropriately provided to healthcare professionals through the package insert.

7.R.3.4 Infusion reaction

The applicant's explanation about infusion reaction associated with cetuximab sarotalocan/laser beam irradiation:

Adverse events related to infusion reaction were tabulated according to MedDRA PT of "infusion related reaction." In Study 102, no infusion reaction occurred.

In the phase IIa part of Study 101, all-Grade infusion reaction occurred in 1 of 30 patients (3.3%, Grade 2 infusion related reaction).²⁷⁾ No fatal or serious infusion reaction, or infusion reaction leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred.

In Studies 101 and 102, prophylaxis with antihistamines and challenge administration of cetuximab were performed to prevent infusion reaction in response to administration of cetuximab sarotalocan. PMDA asked the applicant to explain the necessity of the concerned prophylactic and challenge administration.

The applicant's response:

Cetuximab, a component of cetuximab sarotalocan, is known to have a risk of infusion reaction, and thus, the prophylactic administration against infusion reaction was implemented in Studies 101 and 102. The applicant therefore plans to include in the package insert a precaution statement about prophylaxis

²⁷⁾ One patient enrolled in this study did not receive cetuximab sarotalocan because Grade ≥ 3 infusion reaction occurred in response to the challenge administration.

with antihistamines. The challenge administration of cetuximab, on the other hand, is not recommended for administration of cetuximab (*Ann Oncol.* 2017;28:100-18), and the applicant considers it unnecessary.

PMDA's view:

Although the number of patients experiencing infusion reaction is limited in clinical studies from which data were submitted, cetuximab sarotalocan is an ADC, and for its antibody component, cetuximab, cautions about infusion reaction have been advised. Attention therefore should be paid to infusion reaction when cetuximab sarotalocan is administered. Information about the incidence of infusion reaction in clinical studies should be appropriately provided to healthcare professionals through the package insert, and cautions about prophylactic administration against infusion reaction should be advised. In addition, PMDA accepted the applicant's explanation about challenge administration of cetuximab.

7.R.3.5 Photosensitivity

The applicant's explanation about photosensitivity associated with cetuximab sarotalocan/laser beam irradiation:

Adverse events related to photosensitivity were tabulated according to MedDRA PT of "photosensitivity reaction." No photosensitivity occurred in Study 102.

In the phase I part of Study 101, all-Grade photosensitivity occurred in 1 of 9 patients (11.1%, Grade 2 photosensitivity reaction in 1 patient). No fatal or serious photosensitivity, or photosensitivity leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred.

In the phase IIa part of Study 101, all-Grade photosensitivity occurred in 1 of 30 patients (3.3%, Grade 1 photosensitivity reaction in 1 patient). No fatal or serious photosensitivity, or photosensitivity leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred.

In the phase I and phase IIa parts of Study 101, the time to first onset of photosensitivity was 2 and 4 days, respectively.

In Studies 101 and 102, light-shielding control was in place until no occurrence of skin reaction was confirmed at 4 weeks after administration of cetuximab sarotalocan or in a photosensitivity testing,²⁸⁾ but in light of the following points, the applicant considers it appropriate to keep the light-shielding control in place for 1 week after administration of cetuximab sarotalocan:

- In photosensitivity testing in the phase I part of Study 101 and Study 102, very mild erythema was observed in 2 of 9 patients and 1 of 3 patients, respectively, and time to onset of the concerned event was 4 days and 4 to 14 days in the phase I part of Study 101 and 2 days in Study 102.
- In the above 2 studies, no photosensitivity occurred ≥ 1 week after administration of cetuximab sarotalocan.

²⁸⁾ Light was illuminated with a solar simulator before administration of cetuximab sarotalocan, Day 2 (before laser beam irradiation), Day 4 (only in Study 101), and Day 7. The skin reaction was assessed for 2 signs of erythema (0, no erythema; 1, very mild erythema; 2, definite erythema; 3, moderate to severe erythema; 4, severe erythema to mild crust formation) and oedema (0, no oedema; 1, very mild oedema; 2, mild oedema; 3, moderate oedema; 4, severe oedema). The skin reaction, if still found on Day 7, was assessed every week until it resolved.

PMDA's view:

Because of the limited number of patients experiencing photosensitivity in clinical studies from which data were submitted, it is difficult to draw a clear conclusion on a relationship of cetuximab sarotalocan/laser beam irradiation to photosensitivity. However, taking into account that (a) cetuximab sarotalocan has a photosensitizer as the drug moiety and (b) a phototoxicity study in cynomolgus monkeys suggested that cetuximab sarotalocan might have phototoxicity [see Section 5.7.1], photosensitivity may occur in patients receiving cetuximab sarotalocan, and thus attention should be paid to photosensitivity when cetuximab sarotalocan is administered. Information about the incidence of photosensitivity in clinical studies should be appropriately provided to healthcare professionals through the package insert.

In addition to the above, the safety information about light-shielding control associated with cetuximab sarotalocan/laser beam irradiation are very limited, and it is hardly justified to apply different light-shielding conditions to Studies 101 and 102. Information about light-shielding control measures taken in the clinical studies should be appropriately provided to healthcare professionals to raise cautions.

7.R.3.6 Skin reaction (excluding photosensitivity)

The applicant's explanation about skin reaction (excluding photosensitivity) associated with laser beam irradiation with cetuximab sarotalocan:

Adverse events related to skin reaction were tabulated according to MedDRA PTs of "dermatitis," "dermatitis acneiform," "dermatitis allergic," "dry skin," "erythema," "rash," "rash generalised," "rash maculo-papular," "rash pruritic," "rash pustular," "skin exfoliation," and "skin odour abnormal."

In the phase IIa part of Study 101, all-Grade skin reaction occurred in 17 of 30 patients (56.7%; erythema in 6 patients; rash in 5 patients; dermatitis acneiform, dry skin, rash maculo-papular, and skin odour abnormal in 2 patients each; and dermatitis, dermatitis allergic, rash pruritic, skin exfoliation, and rash pustular in 1 patient each [some patients had multiple events]). Skin reaction leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred in 1 of 30 patients (3.3%, rash in 1 patient). No Grade \geq 3, fatal, or serious skin reaction occurred.

In Study 102, all-Grade skin reaction occurred in 1 of 3 patients (33.3%, rash generalized in 1 patient). No Grade \geq 3, fatal, or serious skin reaction, or skin reaction leading to discontinuation of laser beam irradiation with cetuximab sarotalocan occurred.

In the phase IIa part of Study 101 and Study 102, the median time to first onset of skin reaction (range)²⁶⁾ was 9 days (1-34 days) and 23 days, respectively.

PMDA's view:

All the events of skin reaction associated with cetuximab sarotalocan/laser beam irradiation were at Grade \leq 2 in clinical studies from which data were submitted. However, taking into account that (a) skin reaction occurred at a certain incidence in patients receiving cetuximab sarotalocan/laser beam irradiation and (b) cetuximab, a component of cetuximab sarotalocan, is known to have a risk of severe cutaneous symptom, skin reaction may occur in patients receiving cetuximab sarotalocan/laser beam irradiation, and thus attention should be paid to such events when cetuximab sarotalocan/laser beam

irradiation is performed. Information about the incidence of skin reaction in clinical studies should be appropriately provided to healthcare professionals through the package insert.

7.R.3.7 Safety in patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation

The applicant's explanation about the safety in patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation:

In the phase IIa part of Study 101, 19 of 30 patients (63.3%) received multiple cycles of cetuximab sarotalocan/laser beam irradiation (2 cycles in 7 patients, 3 cycles in 8 patients, and 4 cycles in 4 patients). Table 22 shows the outline of safety by number of cycles of cetuximab sarotalocan/laser beam irradiation in the phase IIa part of Study 101.

Table 22. Outline of safety by number of cycles (phase IIa part of Study 101)

	Number of patients (%)			
	1 cycle n = 11	2 cycles n = 7	3 cycles n = 8	4 cycles n = 4
All adverse events	11 (100)	7 (100)	8 (100)	4 (100)
Grade ≥ 3 adverse events	8 (72.7)	4 (57.1)	5 (62.5)	2 (50.0)
Adverse events leading to death	0	1 (14.3)	1 (12.5)	1 (25.0)
Serious adverse events	5 (45.5)	3 (42.9)	3 (37.5)	2 (50.0)
Adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation	1 (9.1)	2 (28.6)	2 (25.0)	0

In the phase IIa part of Study 101, all-Grade adverse events of which the incidence was $\geq 15\%$ higher in patients treated with multiple cycles than in patients treated with 1 cycle only (numbers of patients treated with multiple cycles, patients treated with 1 cycle only) were fatigue (8 patients [42.1%], 2 patients [18.2%]), oedema peripheral (5 patients [26.3%], 1 patient [9.1%]), dehydration (5 patients [26.3%], 0 patient), oropharyngeal pain (4 patients [21.1%], 0 patient), localised oedema (3 patients [15.8%], 0 patient), stomatitis (3 patients [15.8%], 0 patient), nasal congestion (3 patients [15.8%], 0 patient), and rhinorrhoea (3 patients [15.8%], 0 patient). Similarly, Grade ≥ 3 adverse events of which the incidence was $\geq 10\%$ higher in patients with multiple cycles than in patients with 1 cycle only were localised oedema (2 patients [10.5%], 0 patient), oral pain (2 patients [10.5%], 0 patient), tumour pain (2 patients [10.5%], 0 patient), and tumour haemorrhage (2 patients [10.5%], 0 patient). Adverse events leading to death of which the incidence was $\geq 5\%$ higher in patients with multiple cycles than in patients with 1 cycle only were pneumonia (1¹⁷ patient [5.3%], 0 patient), tumour haemorrhage (1¹⁸ patient [5.3%], 0 patient), and arterial haemorrhage (1¹⁹ patient [5.3%], 0 patient), and a causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for all the events. Serious adverse events of which the incidence was $\geq 10\%$ higher in patients with multiple cycles than in patients with 1 cycle only were tumour haemorrhage (2 patients [10.5%], 0 patient), and a causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for either event. There were no adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation of which the incidence was $\geq 10\%$ higher in patients with multiple cycles than in patients with 1 cycle only. Adverse events reported by ≥ 2 patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation but not by patients treated with 1 cycle only were dehydration in 5 patients (26.3%); oropharyngeal pain in 4 patients (21.1%); localised oedema, stomatitis, nasal congestion, and rhinorrhoea in 3 patients each (15.8%); and application site oedema, chills, nausea, odynophagia, swollen tongue, dermatitis acneiform, dry skin,

rash maculo-papular, dysphonia, dyspnoea, laryngeal oedema, urinary tract infection, and dysarthria in 2 patients each (10.5%).

Although there were adverse events of which the incidence was higher in patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation than in patients treated with 1 cycle only, all of these events were non-serious, and thus multiple cycles is tolerable.

PMDA's view:

Because there were adverse events of which the incidence was higher in patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation than in patients treated with 1 cycle only and adverse events reported only by patients treated with multiple cycles, attention should be paid to such adverse events reported by patients with multiple cycles, and information on the incidences of these events should be appropriately provided to healthcare professionals through the package insert. In addition, although evaluation of the safety in Japanese patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation has limitations owing to absence of such patients in Study 102, multiple cycles of cetuximab sarotalocan/laser beam irradiation can be managed in Japanese patients with cancer as well by taking appropriate measures such as discontinuation of treatment in light of the following points:

- Incidences of serious adverse events did not tend to be evidently higher in patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation than in patients treated with 1 cycle only.
- Single cycle of cetuximab sarotalocan/laser beam irradiation was tolerable in Japanese patients [see Section 7.R.3.1].

7.R.3.8 Safety in patients previously treated with RT

The applicant's explanation about the safety in patients with prior treatment with RT in the lesion:

Patients with the lesion on which the last session of RT had been performed within 4 weeks were excluded from Studies 101 and 102 because the RT-related tissue damage may affect the safety of cetuximab sarotalocan/laser beam irradiation. Clinical study results on the safety of cetuximab sarotalocan/laser beam irradiation in these patients are not available. Eligibility for cetuximab sarotalocan/laser beam irradiation, however, should be determined based on clinical conditions in the organs in the radiation field because severity of RT-related tissue damage and time to recovery from the concerned tissue damage may differ from patient to patient.

PMDA's view:

PMDA largely accepted the above applicant's explanation. Information that patients with the lesion on which the last session of RT had been performed within 4 weeks were excluded from Studies 101 and 102 should be appropriately provided to healthcare professionals using materials.

7.R.4 Indication

The proposed indication of cetuximab sarotalocan was "recurrent head and neck cancer." After submission of this application, however, the applicant proposed that the Indication and Precautions Concerning Indication sections of cetuximab sarotalocan would be changed as shown below:

Indication

Local treatment for advanced or recurrent head and neck cancer

Precautions Concerning Indication

- 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 cetuximab sarotalocan.
- The definitive therapy such as surgical resection or chemoradiotherapy, if feasible, should be performed in preference to cetuximab sarotalocan.
- Cetuximab sarotalocan must be indicated for patients who have received prior standard systemic therapy on metastatic head and neck cancer or who are determined to be ineligible for such therapy by physicians.

On the basis of the results from the review in Sections “7.R.2 Clinical positioning and efficacy” and “7.R.3 Safety” as well as the sections described below, PMDA concluded that the indication of cetuximab sarotalocan should be “Unresectable locally advanced or recurrent head and neck cancer” with the following caution statements included in the Precautions Concerning Indication section:

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to cetuximab sarotalocan.
- The efficacy and safety of adjuvant therapy with cetuximab sarotalocan 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 cetuximab sarotalocan.

7.R.4.1 Patients eligible for cetuximab sarotalocan/laser beam irradiation and indication

The applicant’s explanation about patients eligible for cetuximab sarotalocan/laser beam irradiation and indication:

On the basis of the results from Study 101 [see Sections 7.1.2.1 and 7.R.2], cetuximab sarotalocan/laser beam irradiation is recommended for patients with unresectable locally recurrent head and neck cancer. For patients not included in Study 101, i.e., (a) patients with unresectable locally advanced head and neck cancer and (b) patients with non-squamous cell carcinoma, the clinical study results for cetuximab sarotalocan/laser beam irradiation are not available, however, cetuximab sarotalocan/laser beam irradiation may be indicated for these patients, in light of the following points. For patients with postoperative head and neck cancer who are potentially eligible for adjuvant therapy, cetuximab sarotalocan/laser beam irradiation is not recommended because clinical study results in these patients are not available.

- For the patients who meet the above (a) and have difficulty in receiving standard treatment, cetuximab sarotalocan/laser beam irradiation has a certain clinical significance [see Section 7.R.2.1].
- The patients who meet the above (b) are very rare, accounting for approximately 10% of patients with head and neck cancer overall and receive treatment as done for squamous cell carcinoma (*New Clinical Oncology*. fifth revised edition. Nankodo Co., Ltd.; 2018).

As shown in the above, the applicant proposed the indication of cetuximab sarotalocan as “local treatment for advanced or recurrent head and neck cancer” with the package insert that described details of patients in Studies 101 and 102 in the Clinical Studies section and included the following caution statements 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 cetuximab sarotalocan.
- The definitive therapy such as surgical resection or chemoradiotherapy, if feasible, should be performed in preference to cetuximab sarotalocan/laser beam irradiation.
- Cetuximab sarotalocan must be indicated for patients who have received prior standard systemic therapy on metastatic head and neck cancer or who are determined to be ineligible for such therapy by physicians.

PMDA’s view:

PMDA largely accepted the above applicant’s explanation about the target patients of cetuximab sarotalocan/laser beam irradiation. In Studies 101 and 102, however, the efficacy of cetuximab sarotalocan/laser beam irradiation was evaluated mainly based on results on response rate, and no information about survival benefit have become available. In light of the above, a caution statement should be presented to the effect that the standard treatment must be performed in preference to cetuximab sarotalocan/laser beam irradiation as long as the patient is eligible for the standard treatment.

In addition, regarding use of cetuximab sarotalocan/laser beam irradiation as adjuvant therapy, clinical results on the efficacy and safety are not available, and cetuximab sarotalocan/laser beam irradiation is not recommended for postoperative patients. A caution statement to the above effect should be included in the Precautions Concerning Indication section.

As shown in the above, the indication of cetuximab sarotalocan should be specified as “unresectable locally advanced or recurrent head and neck cancer,” and the package insert should describe details of patients in Studies 101 and 102 in the “Clinical Studies” section and include the following statements in the Precautions Concerning Indication section:

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to cetuximab sarotalocan/laser beam irradiation.
- The efficacy and safety of adjuvant therapy with cetuximab sarotalocan 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 cetuximab sarotalocan.

7.R.5 Dosage and administration

The proposed dosage and administration of cetuximab sarotalocan were “the usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over approximately 2 hours or longer once daily. Non-thermal red light (laser beam) is applied to the lesion approximately 24 ± 4 hours after the end of intravenous infusion.” In addition, after submission of this application, the applicant proposed changes on caution statements about prophylactic administration against infusion reaction in the Precautions Concerning Dosage and Administration section as follows:

- The efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents have not been established.
- The efficacy and safety of ≥5 cycles of the cetuximab sarotalocan procedure have not been established.

- The safety of the cetuximab sarotalocan procedure performed within 4 weeks after the last cycle has not been established.
- To alleviate infusion reaction that may occur during administration of cetuximab sarotalocan, pre-treatment with antihistamines and corticosteroids beforehand is desirable.
- Precautions concerning laser beam irradiation:
 - Non-thermal red light (laser beam) is applied using BioBlade[®] Laser System (Rakuten Medical Japan K.K.). For use of BioBlade[®] Laser System, see the package insert and instructions for use of the concerned device.

On the basis of the results from the review in Sections “7.R.2 Clinical positioning and efficacy” and “7.R.3 Safety” as well as the sections described below, PMDA concluded that the dosage and administration of cetuximab sarotalocan should be modified as “the usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over 2 hours or longer once daily. A laser beam is applied to the lesion 20 to 28 hours after the end of intravenous infusion,” and the following caution statements should be included in the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents have not been established.
- If complete response is not achieved, up to 4 cycles of the procedure consisting of intravenous infusion of cetuximab sarotalocan and subsequent laser beam irradiation to the lesion may be performed at intervals of ≥4 weeks.
- To alleviate infusion reaction that may occur during administration of cetuximab sarotalocan, pre-treatment with antihistamines and corticosteroids should be conducted beforehand.
- Laser beam irradiation should be performed with a semiconductor laser for photodynamic therapy (PDT) manufactured by Rakuten Medical Japan K.K.

7.R.5.1 Dosage and administration of cetuximab sarotalocan

The applicant’s explanation about rationale for the proposed dosage and administration of cetuximab sarotalocan:

In the phase I part of Study 101, a single dose of cetuximab sarotalocan at 160 to 640 mg/m² was intravenously administered followed by laser beam irradiation, and no DLT was observed, demonstrating the tolerability of cetuximab sarotalocan at 640 mg/m² in combination with laser beam irradiation. The phase IIa part of Study 101 and Study 102 were conducted using the dosing regimen established based on the above clinical study results. Clinical usefulness of cetuximab sarotalocan/laser beam irradiation was confirmed in the patients included in these 2 studies [see Sections 7.R.2 and 7.R.3]. Thus, according to these study settings, the dosage and administration of cetuximab sarotalocan were proposed as “the usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over approximately 2 hours or longer once daily. Non-thermal red light (laser beam) is applied to the lesion 24 ± 4 hours after the end of intravenous infusion.” Moreover, the Precautions Concerning Dosage and Administration section will include precaution statements about prophylactic administration against infusion reaction [see Section 7.R.3.5] and a device used for laser beam irradiation.

In addition, for multiple cycles of cetuximab sarotalocan/laser beam irradiation, precaution statements on (a) the upper limit of cycles and (b) the interval between cycles will be included in the Precautions Concerning Dosage and Administration section based on the study settings in the phase IIa part of Study 101 in which of 19 patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation, 4 patients achieved CR, and all patients had no safety problems [see Section 7.R.3.7].

Furthermore, the Precautions Concerning Dosage and Administration section will include a caution statement to the effect that no clinical study results on the efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents are available.

PMDA's view:

PMDA largely accepted the applicant's explanation about the dosing regimen. However, the dosing regimen of cetuximab sarotalocan should be modified as "The usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over 2 hours or longer once daily. A laser beam is applied to the lesion 20 to 28 hours after the end of intravenous infusion."

In addition, the Precautions Concerning Dosage and Administration section should be specified below, in light of results from the review in "7.R.3.7 Safety in patients treated with multiple cycles of cetuximab sarotalocan/laser beam irradiation" and the following points:

- The precaution statements for multiple cycles of cetuximab sarotalocan/laser beam irradiation should cover the upper limit of cycles and interval as well as include a statement to the effect that the procedure may be performed when CR is not achieved in the last cycle, based on the study settings in the phase IIa part of Study 101.
- The precaution statements for prophylactic administration against infusion reaction should refer to administration of not only antihistamines but also corticosteroids based on the study settings in the phase IIa part of Study 101.
- The precaution statement to the effect that the package insert and instructions for use of the medical device for laser beam irradiation should be consulted is not necessary because it is a general statement.

Precautions Concerning Dosage and Administration

- The efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents have not been established.
- If complete response is not achieved, up to 4 cycles of the procedure consisting of intravenous infusion of cetuximab sarotalocan and subsequent laser beam irradiation to the lesion may be performed at intervals of ≥ 4 weeks.
- To alleviate infusion reaction that may occur during administration of cetuximab sarotalocan, antihistamines and corticosteroids should be administered beforehand.
- Laser beam irradiation should be performed with a semiconductor laser for PDT manufactured by Rakuten Medical Japan K.K.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations:

The applicant plans to conduct a post-marketing surveillance in order to investigate the safety of cetuximab sarotalocan/laser beam irradiation in post-marketing clinical use, covering all patients treated with cetuximab sarotalocan/laser beam irradiation and selecting adverse drug reactions and malfunctions as the safety specifications.

The planned sample size for the surveillance was 180 patients in light of the incidences of adverse events in Studies 101 and 102.

The observation period was 6 months after the date of the last practice of cetuximab sarotalocan/laser beam irradiation in light of the time to onset of adverse events in Studies 101 and 102.

PMDA's view:

Because the safety information in Japanese patients receiving cetuximab sarotalocan/laser beam irradiation is limited, the applicant should conduct a post-marketing surveillance covering all patients who have received cetuximab sarotalocan for a specified period after marketing, collect the safety information promptly without bias, and provide the obtained safety information to healthcare professionals immediately.

The safety specifications for this surveillance should include carotid arterial haemorrhage and tumour haemorrhage; swollen tongue and laryngeal oedema; infusion reaction; photosensitivity; and severe skin disorder in light of results from the review in Section "7.R.3 Safety."

The planned sample size and observation period should be reconsidered based on data on the above events selected as the safety specifications of this surveillance.

7.R.7 Proper practices of cetuximab sarotalocan/laser beam irradiation

The applicant's explanation about measures to ensure proper use of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck squamous cell carcinoma in post-marketing clinical use:

Because the experience with cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck squamous cell carcinoma is very limited, a seminar about the procedure of cetuximab sarotalocan/laser beam irradiation is planned to be held for physicians planning to perform the procedure to ensure proper use of cetuximab sarotalocan/laser beam irradiation after the launch. This seminar will provide information about (a) patients eligible for cetuximab sarotalocan/laser beam irradiation, (b) handling of medical devices used for laser beam irradiation (semiconductor laser device, diffuser, needle catheter, etc.), and (c) safety measures for cetuximab sarotalocan/laser beam irradiation.

PMDA accepted the applicant's explanation.

7.2 Adverse events observed in clinical studies

Deaths reported in the safety evaluation data are presented in Section "7.1 Evaluation data." The major adverse events excluding deaths are shown below.

7.2.1 Japanese phase I study (Study 102)

Adverse events were observed in all the patients, and adverse events for which a causal relationship to cetuximab sarotalocan could not be ruled out were observed in all of them. An adverse event reported by ≥ 2 patients was application site pain in 3 patients (100%).

Neither serious adverse events nor adverse events leading to discontinuation of the investigational treatment occurred.

7.2.2 Foreign phase I/IIa study (Study 101)

7.2.2.1 Phase I part

Adverse events were observed in all the patients, and adverse events for which a causal relationship to cetuximab sarotalocan/laser beam irradiation could not be ruled out were observed in all of them. Adverse events reported by ≥ 2 patients were application site pain, cough, and oropharyngeal pain in 3 patients each (33.3%); and application site oedema, fatigue, pyrexia, constipation, dysphagia, oral pain, flushing, hypotension, hypokalaemia, and anxiety in 2 patients each (22.2%).

Serious adverse events occurred in 4 of 9 patients (44.4%). Reported serious adverse events were tumour haemorrhage, tumour pain, oral pain, pneumonia aspiration, dehydration, and depressed level of consciousness in 1 patient each (11.1%). A causal relationship to cetuximab sarotalocan/laser beam irradiation could not be ruled out for tumour haemorrhage, tumour pain, and oral pain in 1 patient each.

No adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred.

7.2.2.2 Phase IIa part

Adverse events were observed in all the patients, and adverse events for which a causal relationship to cetuximab sarotalocan/laser beam irradiation could not be ruled out were observed in 25 of 30 patients (83.3%). Adverse events with an incidence of $\geq 20\%$ were fatigue in 10 patients (33.3%), dysphagia in 7 patients (23.3%), and oedema peripheral, constipation, and erythema in 6 patients each (20.0%).

Serious adverse events occurred in 13 of 30 patients (43.3%). Serious adverse events reported by ≥ 2 patients were pneumonia in 3 patients (10.0%) and tumour haemorrhage in 2 patients (6.7%), and a causal relationship to cetuximab sarotalocan/laser beam irradiation was denied for all of these.

Adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation occurred in 5 of 30 patients (16.7%). There were no adverse events leading to discontinuation of cetuximab sarotalocan/laser beam irradiation reported by ≥ 2 patients.

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 inspection is currently ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

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

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

On the basis of the data submitted, PMDA has concluded that cetuximab sarotalocan/laser beam irradiation has a certain level of efficacy in the treatment of unresectable locally advanced or recurrent head and neck cancer, and that cetuximab sarotalocan/laser beam irradiation has acceptable safety in view of its benefits. Cetuximab sarotalocan/laser beam irradiation is a treatment procedure that is expected to damage tumor cells by exciting cetuximab sarotalocan bound to EGFR expressed on tumor cell membrane through laser beam irradiation at 690 nm with a semiconductor laser device and is considered to be clinically meaningful, offering a treatment option for patients with unresectable locally advanced or recurrent head and neck cancer. In addition, PMDA considers that the indication, dosage and administration, and post-marketing investigations should be further reviewed.

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

Review Report (2)

August 18, 2020

Product Submitted for Approval

Brand Name	Akalux IV Infusion 250 mg
Non-proprietary Name	Cetuximab Sarotalocan Sodium (Genetical Recombination)
Applicant	Rakuten Medical Japan K.K.
Date of Application	March 26, 2020

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 a foreign phase I/IIa study (Study 101) of cetuximab sarotalocan/laser beam irradiation in patients with unresectable locally recurrent head and neck squamous cell carcinoma, the response rate [95% CI] (%) centrally assessed according to revised RECIST ver.1.1 was 43.3 [25.5, 62.6].

In view of the discussions presented in Section “7.R.2 Clinical positioning and efficacy” of the Review Report (1), the above result on the response rate, and the following points, PMDA has concluded that cetuximab sarotalocan/laser beam irradiation has a certain level of efficacy in patients with unresectable locally advanced or recurrent head and neck cancer and should be positioned as a treatment option for such patients:

- Local lesions in patients with unresectable locally recurrent head and neck cancer may cause pathological conditions remarkably compromising patients’ QOL, such as dysphagia, malnutrition, airway narrowing, aspiration, and fistula formation, and local control of the lesions has a certain clinical significance.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

In view of the discussions presented in Section “7.R.3 Safety” of the Review Report (1), PMDA has concluded that adverse events requiring special attention in treatment with cetuximab sarotalocan/laser

beam irradiation in patients with unresectable locally recurrent head and neck cancer are haemorrhage, swelling, infusion reaction, photosensitivity, and skin reaction (except for photosensitivity).

In addition, although attention should be paid to the above adverse events when cetuximab sarotalocan/laser beam irradiation is performed, PMDA has concluded that cetuximab sarotalocan/laser beam irradiation is tolerable provided that physicians with sufficient knowledge and experience in cancer chemotherapy and photodynamic therapy take appropriate measures such as monitoring and controlling the adverse events.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Indication

In view of the discussions presented in Section “7.R.4 Indication” of the Review Report (1), PMDA has concluded that the indication of cetuximab sarotalocan should be “unresectable locally advanced or recurrent head and neck cancer,” and the package insert should describe details of patients in Studies 101 and 102 in the Clinical Studies section and include the following statements in the Precautions Concerning Indication section.

Precautions Concerning Indication

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to cetuximab sarotalocan/laser beam irradiation.
- The efficacy and safety of adjuvant therapy with cetuximab sarotalocan 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 cetuximab sarotalocan.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to establish the Indication and Precautions Concerning Indication sections as described above, and the applicant accepted the instruction.

1.4 Dosage and administration

In view of the discussions presented in Section “7.R.5 Dosage and administration” of the Review Report (1), PMDA has concluded that the dosage and administration of cetuximab sarotalocan should be specified as “the usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over 2 hours or longer once daily. A laser beam is applied to the lesion 20 to 28 hours after the end of intravenous infusion,” and the following caution statements should be included in the Precautions Concerning Dosage and Administration section:

Precautions Concerning Dosage and Administration

- The efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents have not been established.

- If complete response is not achieved, up to 4 cycles of the procedure consisting of intravenous infusion of cetuximab sarotalocan and subsequent laser beam irradiation to the lesion may be performed at intervals of ≥ 4 weeks.
- To alleviate infusion reaction that may occur during administration of cetuximab sarotalocan, antihistamines and corticosteroids should be administered beforehand.
- Laser beam irradiation should be performed with a semiconductor laser for PDT manufactured by Rakuten Medical Japan K.K.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- Because cetuximab sarotalocan is used in combination with a semiconductor laser device, it is important to provide information about conditions of the laser beam irradiation to healthcare professionals through the package insert so that cetuximab sarotalocan/laser beam irradiation will be appropriately performed on unresectable locally advanced or recurrent head and neck cancer.

PMDA's view:

In view of the importance of information about conditions of the laser beam irradiation as commented above, the Precautions Concerning Dosage and Administration section should be established as shown below:

Precautions Concerning Dosage and Administration

- The efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents have not been established.
- If complete response is not achieved, up to 4 cycles of the procedure consisting of intravenous infusion of cetuximab sarotalocan and subsequent laser beam irradiation to the lesion may be performed at intervals of ≥ 4 weeks.
- To alleviate infusion reaction that may occur during administration of cetuximab sarotalocan, antihistamines and corticosteroids should be administered beforehand.
- A semiconductor laser for PDT approved for use in targeting cancer in combination with cetuximab sarotalocan should be used to perform laser beam irradiation. For conditions of the laser beam irradiation, see the instructions for use of the concerned medical device.

PMDA instructed the applicant to establish the Dosage and Administration and Precautions Concerning Dosage and Administration sections as described above, and the applicant accepted the instruction.

1.5 Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance covering all the patients treated with cetuximab sarotalocan/laser beam irradiation to investigate the safety of cetuximab sarotalocan/laser beam irradiation in post-marketing clinical use. For the surveillance, the planned sample size is 180 patients, and the observation period is 6 months after the date of the last practice of cetuximab sarotalocan/laser beam irradiation.

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that the applicant should conduct a post-marketing surveillance

covering all patients who have received cetuximab sarotalocan for a specified period after marketing, collect the safety information promptly without bias, and provide the obtained safety information to healthcare professionals immediately.

In addition, PMDA has concluded on the surveillance plan as follows:

- The safety specifications of the surveillance should include carotid arterial haemorrhage and tumour haemorrhage; swollen tongue and laryngeal oedema; infusion reaction; photosensitivity; and severe skin disorder.
- The planned sample size and observation period should be reconsidered based on the incidences of the above events in clinical studies selected as the safety specifications of this surveillance.

Furthermore, because mastery of technique and knowledge about cetuximab sarotalocan/laser beam irradiation is required for proper practices of cetuximab sarotalocan/laser beam irradiation, a seminar about the procedure of cetuximab sarotalocan/laser beam irradiation should be held for physicians planning to perform the procedure after marketing. This seminar should provide information about (a) patients eligible for cetuximab sarotalocan/laser beam irradiation, (b) handling of medical devices used for laser beam irradiation (semiconductor laser device, diffuser, needle catheter, etc.), and (c) safety measures for cetuximab sarotalocan/laser beam irradiation.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

On the basis of the discussions above, PMDA instructed the applicant to reconsider the surveillance plan and take appropriate measures to ensure proper practices of cetuximab sarotalocan/laser beam irradiation.

The applicant's response:

- The safety specifications of the surveillance will include carotid arterial haemorrhage and tumour haemorrhage; swollen tongue and laryngeal oedema; infusion reaction; photosensitivity; and severe skin disorder.
- The planned sample size and observation period of the surveillance will be specified as 180 patients and a period from the first treatment to 6 months after the last treatment based on the incidences of the events in the clinical studies selected as the safety specifications.
- For proper practices of cetuximab sarotalocan/laser beam irradiation, necessary measures such as establishing requirements for physicians and facilities will be taken in collaboration with relevant academic societies.

PMDA accepted the applicant's response.

In addition, in view of the discussion above, PMDA has concluded that the risk management plan (draft) for cetuximab sarotalocan should include the safety specifications presented in Table 23, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 24 and 25.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
<ul style="list-style-type: none"> • Carotid arterial haemorrhage and tumour haemorrhage • Swollen tongue and laryngeal oedema • Infusion reaction 	<ul style="list-style-type: none"> • Photosensitivity • Severe skin disorder 	None
Efficacy specifications		
None		

Table 24. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
<ul style="list-style-type: none"> • Early post-marketing phase vigilance • General use-results survey (all-case surveillance) • Post-marketing clinical study (extension study of Study 301) 	None	<ul style="list-style-type: none"> • Disseminate information obtained from early post-marketing phase vigilance • Organize and disseminate materials for patients • Establish conditions of use

Table 25. Outline of use-results survey (draft)

Objective	To investigate the safety of cetuximab sarotalocan in clinical use
Survey method	All-case surveillance study
Population	All patients who have received cetuximab sarotalocan
Observation period	Period from the first treatment to 6 months after the last treatment
Planned sample size	180 patients
Main survey items	Safety specifications: Carotid arterial haemorrhage and tumour haemorrhage; swollen tongue and laryngeal oedema; infusion reaction; photosensitivity; and severe skin disorder Other main survey items: Patient characteristics (age, sex, complications, medical history, etc.), use status of cetuximab sarotalocan, use status of medical devices, concomitant drugs, adverse events, etc.

1.6 Others

1.6.1 Shelf life of drug product

The applicant's explanation about shelf life of the drug product:

For 1 batch of the drug product manufactured by the proposed process, stability data until 9 months of storage under the long-term condition were replaced by the data until 12 months, which showed no changes in quality attributes throughout the period as with 2 batches of the drug product manufactured by Process ■.

On the basis of the above, the shelf life of 12 months is established for the drug product when stored using a chlorobutyl rubber stopper and a brown glass vial as the primary container at 2°C to 8°C under protection from light with an aluminum-laminated film bag and a carton.

PMDA accepted the applicant's explanation.

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

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

The new drug application data were subjected to a document-based 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.

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

The new drug application data (CTD 5.3.5.2.2) 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. On the basis of the inspection, which confirmed that the clinical studies were conducted in accordance with GCP overall, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The following finding, however, was noted with the sponsor (clinical trial in-country representative), although this would hardly affect the overall study evaluation. The finding was communicated to the sponsor (clinical trial in-country representative) as finding requiring corrective action.

Finding requiring corrective action

Sponsor (clinical trial in-country representative)

- At start of the clinical study, there were no procedures for preparation of study protocol, preparation of investigator's brochure, compensation for study-related injury available for subjects, and operations for record retention.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions, provided that the package insert available after marketing includes appropriate precautions and information for proper use; and cetuximab sarotalocan is properly used by a physician with sufficient knowledge and experience in cancer chemotherapy and photodynamic therapy at a medical institution capable of appropriately dealing with emergencies. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product, and drug product and its drug substance are both classified as powerful drugs.

Indication

Unresectable locally advanced or recurrent head and neck cancer

Dosage and Administration

The usual adult dosage is 640 mg/m² (body surface) of cetuximab sarotalocan sodium (genetical recombination) administered as an intravenous infusion over 2 hours or longer once daily. A laser beam is applied to the lesion 20 to 28 hours after the end of intravenous infusion.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics

of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

3. The applicant is required to provide data on the efficacy and safety of a treatment procedure with the product from the ongoing phase III study in patients with unresectable locally recurrent head and neck cancer to healthcare professionals in an appropriate manner.
4. The applicant is required to take necessary measures to ensure that the product is used only by physicians who have been trained for the treatment procedure with the product and have sufficient knowledge and experience in the treatment procedure.

Warnings

Cetuximab sarotalocan should be administered only to patients considered to be eligible for the therapy with cetuximab sarotalocan by a physician with sufficient knowledge and experience in cancer chemotherapy and photodynamic therapy at a medical institution capable of appropriately dealing with emergencies. Prior to treatment, the benefits and risks of the therapy should be thoroughly explained to the patient or their family member, and consent should be obtained.

Contraindications

1. Patients with a history of hypersensitivity to any of the ingredients of Akalux IV Infusion 250 mg
2. Patients with tumor invasion in the carotid artery (Carotid arterial haemorrhage or tumour haemorrhage may occur in association with tumor regression or necrosis.)

Precautions Concerning Indication

1. The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to cetuximab sarotalocan/laser beam irradiation.
2. The efficacy and safety of adjuvant therapy with cetuximab sarotalocan 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 cetuximab sarotalocan.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of cetuximab sarotalocan in combination with the other antineoplastic agents have not been established.
2. If complete response is not achieved, up to 4 cycles of the procedure consisting of intravenous infusion of cetuximab sarotalocan and subsequent laser beam irradiation to the lesion may be performed at intervals of ≥ 4 weeks.
3. To alleviate infusion reaction that may occur during administration of cetuximab sarotalocan, pre-treatment with antihistamines and corticosteroids should be conducted beforehand.
4. A semiconductor laser for PDT approved for use in targeting cancer in combination with cetuximab sarotalocan should be used to perform laser beam irradiation. For conditions of the laser beam irradiation, see the instructions for use of the concerned medical device.

List of Abbreviations

ADC	antibody-drug conjugate
ADCC	antibody dependent cellular cytotoxicity
Application	marketing application
ATP	adenosine triphosphate
BNCT	boron neutron capture therapy
BSE	bovine spongiform encephalopathy
CAL	cells at the limit of <i>in vitro</i> cell age
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
Cetuximab	cetuximab (genetical recombination)
Cetuximab sarotalocan	cetuximab sarotalocan sodium (genetical recombination)
Cetuximab sarotalocan/ laser beam irradiation	administration of cetuximab sarotalocan followed by laser beam irradiation
CEX-LC	cation exchange liquid chromatography
CheckMate 141 study	ONO-4538-11/CA209141 study
CI	confidence interval
CQA	critical quality attribute
CR	complete response
CRT	chemoradiotherapy
DAR	drug-to-antibody ratio
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DTX	docetaxel hydrate
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
GC	gas chromatography
GGT	gamma-glutamyltransferase
HCP	host cell protein
HER	human epidermal growth factor receptor
HPLC	high performance liquid chromatography
HRP	horseradish peroxidase
IC	investigator's choice
icIEF	image capillary isoelectric focusing
Ig	immunoglobulin
IR	infrared absorption spectrum
IR700 NHS ester	silicate(4-),[2,5-dioxo-1-pyrrolidinyl 6-[[[3-[(29 <i>H</i> ,31 <i>H</i> -phthalocyanin-1-yl κN^{29} , κN^{30} , κN^{31} , κN^{32})oxy]propoxy]carbonyl]amino]hexanoato(2-)]bis [N-[3-[(hydroxy- κO)dimethylsilyl]propyl]-3-sulfo- <i>N,N</i> -bis(3-sulfopropyl)-1-propanaminiumato(4-)]-,sodium (1:4)
IR700 carboxylate	silicate(5-),bis[N-[3-[(hydroxy- κO)dimethylsilyl]propyl]-3-sulfo- <i>N,N</i> -bis(3-sulfopropyl)-1-propanaminiumato(4-)]][6-[[[3-(29 <i>H</i> ,31 <i>H</i> -phthalocyanin-1-yl κN^{29} , κN^{30} , κN^{31} , κN^{32})oxy]propoxy]carbonyl]amino]hexanoato(3-)]-,sodium (1:5)
LC	liquid chromatography
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MF	master file
MFI	mean fluorescence intensity
MTX	methotrexate
NE	not evaluable
Nivolumab	nivolumab (genetical recombination)
NMR	nuclear magnetic resonance spectrum
OS	overall survival

PD	progressive disease
Pembrolizumab	pembrolizumab (genetical recombination)
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
QbD	quality by design
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SD	stable disease
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC-LC	size exclusion liquid chromatography
Study 101	RM-1929-101 study
Study 102	RM-1929-102 study
Study 301	RM-1929-301 study
WCB	working cell bank