

Report on the Deliberation Results

May 14, 2015

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

| | |
|------------------------|----------------------------------|
| [Brand name] | Laserphyrin 100 mg for Injection |
| [Non-proprietary name] | Talaporfin Sodium (JAN*) |
| [Applicant] | Meiji Seika Pharma Co., Ltd. |
| [Date of application] | September 22, 2014 |

[Results of deliberation]

In the meeting held on April 24, 2015, the Second Committee on New Drugs concluded that the application for partial change of 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 re-examination period for the product is 10 years.

[Conditions for approval]

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Take necessary measures to ensure that the product is administered only by physicians with sufficient knowledge and experience in photodynamic therapy who have undergone a training session on photodynamic therapy with the product.

**Japanese Accepted Name (modified INN)*

Review Report

April 13, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

| | |
|------------------------------------|--|
| [Brand name] | Laserphyrin 100 mg for Injection |
| [Non-proprietary name] | Talaporfin Sodium |
| [Applicant] | Meiji Seika Pharma Co., Ltd. |
| [Date of application] | September 22, 2014 |
| [Dosage form/Strength] | Lyophilized powder for solution for injection: Each vial contains 100 mg of talaporfin sodium. |
| [Application classification] | Prescription drug (4) Drug with a new indication |
| [Items warranting special mention] | Orphan drug (Drug Designation No.330 of 2014 [26 <i>yaku</i>]; PFSB/ELD Notification No.0317-2 dated March 17, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) |
| [Reviewing office] | Office of New Drug V |

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Results

April 13, 2015

[Brand name] Laserphyrin 100 mg for Injection
[Non-proprietary name] Talaporfin Sodium
[Applicant] Meiji Seika Pharma Co., Ltd.
[Date of application] September 22, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy has been demonstrated and its safety is acceptable in view of its observed benefits. Oesophageal stenosis and oesophageal perforation occurring in patients receiving the product should be further evaluated in the post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indications and dosage and administration as shown below, with the following conditions for approval.

[Indications]

- (1) Early-stage lung cancer (Stage 0 or I) treatable with laser irradiation in patients ineligible for other radical interventions including surgical resection, or in patients who require the preservation of pulmonary function but cannot receive other treatments. The entire tumor must be observable endoscopically.
- (2) Primary malignant brain tumor (only in patients who undergo resection of brain tumor)
- (3) Local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy

(Words underlined are additions.)

[Dosage and administration]

- (1) Early-stage lung cancer, and local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy

The usual adult dosage is 40 mg/m² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection.

- (2) Primary malignant brain tumor

The usual adult dosage is 40 mg/m² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 22 and 26 hours after intravenous injection.

(Words underlined are additions.)

[Conditions for approval]

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Take necessary measures to ensure that the product is administered only by physicians with sufficient knowledge and experience in photodynamic therapy who have undergone a training session on photodynamic therapy with the product.

Review Report (1)

March 10, 2015

I. Product Submitted for Registration

| | |
|------------------------|--|
| [Brand name] | Laserphyrin 100 mg for Injection |
| [Non-proprietary name] | Talaporfin Sodium |
| [Applicant] | Meiji Seika Pharma Co., Ltd. |
| [Date of application] | September 22, 2014 |
| [Dosage form/Strength] | Lyophilized powder for solution for injection: Each vial contains 100 mg of talaporfin sodium. |
| [Proposed indication] | (1) Early-stage lung cancer (Stage 0 or I) treatable with laser irradiation in patients ineligible for other radical interventions including surgical resection, or in patients who require the preservation of pulmonary function but cannot receive other treatments. The entire tumor must be observable endoscopically. (2) Primary malignant brain tumor (only in patients who undergo resection of brain tumor) (3) <u>Local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy</u> (Words underlined are additions.) |

| | |
|--------------------------------------|--|
| [Proposed dosage and administration] | (1) Early-stage lung cancer, <u>and local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy</u> The dosage is 40 mg/m ² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection. (2) Primary malignant brain tumor The usual adult dosage is 40 mg/m ² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 22 and 26 hours after intravenous injection. (Words underlined are additions.) |
|--------------------------------------|--|

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

Since this application was filed for an additional indication, the applicant did not submit “data relating to quality” or non-clinical pharmacokinetic study data.

1. Origin or history of discovery, use in foreign countries, and other information

1.(1) Summary of the product submitted for registration

Photodynamic therapy (PDT) of malignant tumors is a treatment involving administration of a photosensitizing agent that preferentially accumulates in tumor cells, followed by irradiation of the tumor tissues with laser light. The photosensitizing agent absorbs laser light and produces excited singlet oxygen molecules that damage tumor cells and tumor vessels nonspecifically, thereby suppressing tumor growth.

Talaporfin sodium, a plant chlorophyll-derived photosensitizer for PDT, was developed by Nippon Petrochemicals Co., Ltd. (currently JX Nippon Oil & Energy Corporation). Talaporfin sodium was approved for early-stage lung cancer in October 2003 and for primary malignant brain tumor in September 2013.

1.(2) History of development

As of January 2015, talaporfin sodium has not been approved or submitted for approval in any country or region outside Japan.

In Japan, a phase II study (Study KUTR-015-2) started in October 2012 in patients with local residual/recurrent oesophageal carcinoma, to assess the efficacy and safety of PDT with talaporfin sodium, in view of the results of a clinical research that had been conducted in the same patient population to assess the efficacy and safety of PDT with talaporfin sodium.

The applicant filed an application for partial change based on the results of Study KUTR-015-2, in order to add “local residual/recurrent oesophageal carcinoma” to the approved indications.

The photodynamic (PD) laser and EC-PDT probe, which are used to perform PDT with talaporfin sodium for oesophageal carcinoma, were developed by Panasonic Healthcare Co., Ltd. In December 2014, Panasonic Healthcare Co., Ltd. filed an application for marketing approval of the PD laser and EC-PDT probe with the intended use and indications as shown below. Talaporfin sodium was designated as an orphan drug in March 2014 (Drug Designation No.330 of 2014 [26 *yaku*]) and PDT semiconductor laser (PDT laser and EC-PDT probe) as an orphan medical device in September 2014 (Device Designation No.25 of 2014 [26 *ki*]). Both the drug and device were granted the designation for the intended indication of “local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy.”

PD laser

1. Intended use

The product is a laser device intended to be used for photodynamic therapy. In photodynamic therapy, a tumor-seeking photosensitizer is injected intravenously. The photosensitizer, accumulating in the tumor,

is irradiated with laser light and thereby activated to kill the tumor cells. The product is used with the following drug:

| | |
|--------------------------------|----------------------------------|
| Marketing authorization holder | Meiji Seika Pharma Co., Ltd. |
| Non-proprietary name | Talaporfin Sodium |
| Brand name | Laserphyrin 100 mg for Injection |

2. Indications

The product is used for photodynamic therapy in patients with local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy.

EC-PDT probe

The product is used for photodynamic therapy in patients with local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy.

2. Non-clinical data

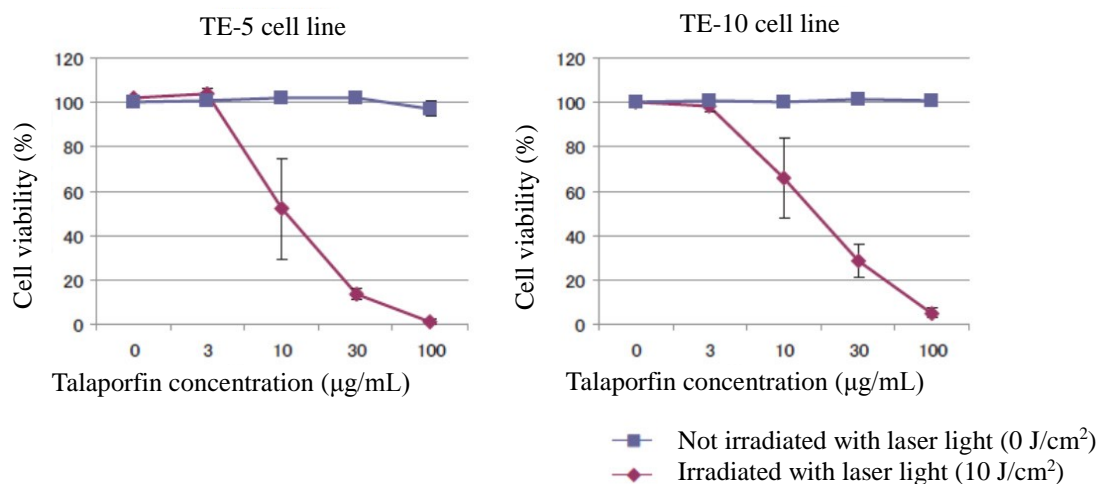
2.(i) Summary of pharmacology studies

2.(i).A *Summary of the submitted data*

Primary pharmacodynamics

2.(i).A.(1) **Effects on oesophageal carcinoma cell line (Report, *In vitro* cytocidal effects of PDT with Laserphyrin on oesophageal carcinoma cells)**

The antiproliferative effect of talaporfin sodium-mediated PDT against human oesophageal carcinoma cell lines TE-5 and TE-10 was assessed based on redox dye-based absorption as an indicator. Each cell line was treated with talaporfin sodium (0, 3, 10, 30, or 100 µg/mL) for 24 hours. Talaporfin sodium was then removed from the medium, and cells were irradiated with laser light (with a fluence of 10 J/cm²). The diagrams below show cell viability at 48 hours after laser irradiation (cell viability = the light absorption rate at each concentration, expressed as a percentage of the light absorption rate in the control cells [100%]. The control cells were not treated with talaporfin sodium or irradiated with laser light).



Antiproliferative effect of talaporfin sodium-mediated PDT against human oesophageal carcinoma cell lines
Mean ± standard deviation; n = 3

The applicant explained that the above results show that talaporfin sodium-mediated PDT exerted antiproliferative effects on tumor cells of oesophageal carcinoma.

2.(i).A.(2) *In vivo* antiproliferative effects of additional laser irradiation on tumor cells (Report

In the clinical study conducted in patients with local residual/recurrent oesophageal carcinoma, patients found to have residual tumor on the day following the initial PDT underwent additional laser irradiation, out of concern that the tumor may not have been appropriately irradiated during the initial PDT [see “3.(i).A. Evaluation data. Japanese phase II study”]. Because of this, an *in vivo* study was conducted to assess the effect of additional irradiation by comparing “the group irradiated with laser light on Day 1 (Group 2 in the table below)” and “the group irradiated with laser light on Day 2, but not on Day 1 (Group 4 in the table below).” A summary of the *in vivo* study is presented below.

Mice were subcutaneously transplanted with murine Meth-A fibrosarcoma tissue. When the thickness of the transplanted tumor became ≥ 7 mm, the mice were given talaporfin sodium on Day 1 or Day 2 (see the table below). At 2 hours after administration of talaporfin sodium, the tumor was irradiated with laser light (with a fluence of 100 J/cm²). An additional dose of talaporfin sodium was administered before additional laser irradiation to ensure that plasma talaporfin concentration at the additional irradiation was approximately half of that at the initial irradiation, taking into account findings including the following: In mice, the terminal phase half-life of talaporfin in plasma is as short as approximately 0.6 to 5.0 hours, but in humans, plasma talaporfin concentration at additional irradiation decreases to approximately half of that at the initial irradiation (see “Review Report of Laserphyrin 100 mg for Injection” dated August 21, 2003 [published in Japanese only]).

The tumor irradiated with laser light was excised from each mouse on Day 2 or Day 3 after the thickness of the transplanted tumor became ≥ 7 mm, and the depth of tumor necrosis was measured. As shown in

the table below, the depth was similar in both Groups 2 and 4. The applicant explained that the results suggested that laser irradiation on Day 2, when plasma talaporfin concentration decreases to approximately half of that on Day 1, has the same level of effect as laser irradiation on Day 1.

Antiproliferative effects of additional laser irradiation on tumor cells in mice subcutaneously transplanted with murine Meth-A fibrosarcoma tissue

| Group | Day 1 | | Day 2 | | Timing of necropsy | Depth of tumor necrosis (mm) |
|-------|--------------------------------|------------------------------|--------------------------------|------------------------------|------------------------|------------------------------|
| | Talaporfin sodium dose (mg/kg) | PDT (100 J/cm ²) | Talaporfin sodium dose (mg/kg) | PDT (100 J/cm ²) | | |
| 1 | 0 | Not irradiated | 0 | Not irradiated | Day 3 | – |
| 2 | 5 | Irradiated | 0 | Not irradiated | Day 2 (24 h after PDT) | 4.7 ± 0.8 |
| 3 | 5 | Irradiated | 0 | Not irradiated | Day 3 (48 h after PDT) | 5.0 ± 0.8 |
| 4 | 5 | Not irradiated | 2.5 | Irradiated | Day 3 (24 h after PDT) | 5.2 ± 0.7 |
| 5 | 5 | Irradiated | 2.5 | Irradiated | Day 3 (24 h after PDT) | 4.8 ± 1.0 |

Mean value ± standard error (n = 5 in Groups 1, 2, and 3; n = 4 in Groups 4 and 5)

2.(i).B Outline of the review by PMDA

PMDA concluded that talaporfin sodium-mediated PDT is expected to be effective in the treatment of oesophageal carcinoma, based on the submitted data for the current application and the fact that the antiproliferative effect of talaporfin sodium-mediated PDT on malignant tumors had been confirmed in the review of talaporfin sodium for the already approved indications (see “Review Report of Laserphyrin 100 mg for Injection” dated August 21, 2003).

2.(ii) Summary of toxicology studies

2.(ii).A Summary of the submitted data

In the toxicology studies, normal saline was used as a solvent.

2.(ii).A.(1) Effects of PDT on the esophagus in dogs (Reference data, non-GLP study)

A single dose of 20 mg/kg of talaporfin sodium was administered intravenously to male dogs (n = 3/group), and the lower esophagus (approximately 5 cm rostral to the esophagogastric junction) was irradiated with laser light approximately 1 hour later under anesthesia (with a fluence of 25, 50, or 100 J/cm²). The effect of the difference in fluence on the esophagus was assessed on post-PDT days 1 to 7. Endoscopic evaluation was also performed in this study.

No animals died or were sacrificed moribund during the study period as a result of administration of talaporfin sodium or laser irradiation.

Findings observed in all groups include body weight decreased; vomiting; reddening, white lumps, erosion, and ulcer of the oesophageal mucosa, mainly in the irradiated area; necrosis, haemorrhage, fibrosis, and inflammatory cell infiltration in the oesophageal mucosa to serosa; necrosis of alveolar

walls; pulmonary alveolar haemorrhage; and fibrin deposit and other inflammatory changes. Findings observed in the groups irradiated with $\geq 50 \text{ J/cm}^2$ include decreased food consumption, haemorrhage in the oesophageal mucosa, inflammatory changes in extraserosal tissues in the esophagus, adhesion between the oesophageal serosa and the aorta, necrosis and haemorrhage of adhered aorta, and fibrosis in the pleura. The damaged area at the irradiated site increased with increasing fluence.

2.(ii).A.(2) Effects of additional irradiation with laser light

In the study of mice subcutaneously transplanted with murine Meth-A fibrosarcoma tissue to assess antiproliferative effects of additional irradiation with laser light [see “2.(i).A.(2) *In vivo* antiproliferative effects of additional laser irradiation on tumor cells”], the safety of additional irradiation was investigated by comparing the results of Group 3 (PDT performed only on Day 1) and Group 5 (PDT performed on Days 1 and 2).

During the study period, no deterioration in general condition, deaths, or sacrifice of moribund animals occurred as a result of administration of talaporfin sodium or irradiation with laser light. Both groups showed dark red, black, or white color change on the subsurface or surface of tumors, and necrosis on the surface skin side of the tumor mass. The depth of necrosis was similar in Groups 3 and 5 (5.0 ± 0.8 mm in Group 3 [PDT only on Day 1]; 4.8 ± 1.0 mm in Group 5 [PDT on Days 1 and 2]). Mild necrosis of peritumoral skin was observed in 1 animal each in both groups. These results demonstrated that additional irradiation of tumor cells causes no serious safety concern.

2.(ii).B Outline of the review by PMDA

PMDA concluded that the clinical use of talaporfin sodium poses no problem, based on the evaluation of the submitted non-clinical toxicity data.

3. Clinical data

3.(i) Summary of clinical efficacy and safety

3.(i).A Summary of the submitted data

The applicant submitted the efficacy and safety evaluation data (a Japanese phase II clinical study) and reference data (a Japanese clinical research).

Clinical studies for efficacy and safety evaluation

| Data class | Location | Study Identifier | Phase | Target population | Enrolled | Dosage regimen | Primary endpoints |
|-----------------|----------|------------------|-------|--|-------------|---|--------------------|
| Evaluation data | Japan | KUTR-015-2 | II | Patients with local residual/recurrent oesophageal carcinoma after CRT or RT | 26 patients | Single intravenous injection of talaporfin sodium 40 mg/m ² *1 | Efficacy Safety |
| Reference data | Japan | KUTR-015-1 | I/II | Patients with local residual/recurrent oesophageal carcinoma after CRT or RT | 19 patients | Single intravenous injection of talaporfin sodium 40 mg/m ² *2 | Safety Efficacy |

CRT, chemoradiotherapy; RT, radiotherapy

*1 The lesion was irradiated with laser light (with a fluence of 100 J/cm²) using a semiconductor laser device (PNL6405EPG) 4 to 6 hours after administration of talaporfin sodium (and additionally, 22 to 32 hours after administration, if needed).

*2 The lesion was irradiated with laser light (with a fluence of 50, 75, or 100 J/cm²) using a semiconductor laser device (PD laser) 4 to 6 hours after administration of talaporfin sodium (and additionally, the next day, if needed).

The clinical study and clinical research are outlined below.

Main adverse events, other than death, reported in the study or research are discussed in “3.(ii) Adverse events reported in clinical studies.”

Evaluation data

Japanese phase II study (5.3.5.2-01, Study KUTR-015-2 [November 2012 to May 2014])

An open-label, uncontrolled study was conducted in patients with local residual/recurrent oesophageal carcinoma after chemoradiotherapy (CRT) or radiotherapy (RT)*¹ (target sample size, 25 subjects) at 7 study centers in Japan to assess the efficacy and safety of talaporfin sodium-mediated PDT.

In this study, subjects received a single intravenous injection of 40 mg/m² talaporfin sodium. Four to 6 hours after administration of talaporfin sodium, the local residual/recurrent lesion was irradiated with 664-nm laser light (with a fluence of 100 J/cm², and a fluence rate of 150 mW/cm²) with a semiconductor laser device. Lesions were endoscopically observed on the day following administration of talaporfin sodium and laser irradiation. If any residual lesion was detected, additional laser irradiation was performed between 22 and 32 hours after administration of talaporfin sodium.

All 26 subjects enrolled in the study were included in the efficacy analysis population, which was the full analysis set (FAS). All 26 subjects who received talaporfin sodium were included in the safety analysis population.

As for efficacy, local complete response (L-CR)^{*2} rate as assessed by central review (the primary endpoint) was 88.5% (95% confidence interval [CI]: 69.8%, 97.6%) (23 of 26 subjects). The probability^{*3} of L-CR rate exceeding 15%, the predefined threshold,^{*4} was 100%.

Safety data showed that no adverse events resulted in death within 29 days of administration of talaporfin sodium.

*1 Patients with histologically confirmed oesophageal carcinoma unresectable by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) who did not wish to, or cannot, undergo surgical resection.

*2 Patients meeting all of the following criteria were judged to have an L-CR:

(a) Endoscopy does not show evident residual tumor;

(b) Endoscopy shows scarring at the treated area; and

(c) Cancer cells have not been pathologically detected in tissue biopsy

*3 In this study, treatment was judged to be effective if L-CR rate in patients undergoing talaporfin sodium-mediated PDT exceeded 15%, the predefined threshold, with a probability of >97.5%, based on the Bayesian statistical approach. The prior distribution was a beta distribution: Beta(1, 1), and the likelihood was a binomial distribution.

*4 This threshold was established based on the results from a clinical study of chemotherapy in patients with residual/recurrent oesophageal carcinoma after CRT (*Cancer Chemother Pharmacol* 2011;67:1265-72).

Reference data

Japanese clinical research (5.3.5.2-02 and 5.3.5.2-03, Study KUTR-015-1 [September 2010 to 2011])

A clinical research was conducted in patients with local residual/recurrent oesophageal carcinoma after CRT or RT at 7 study centers in Japan, to assess the recommended fluence (phase I part) and the efficacy and safety of talaporfin sodium-mediated PDT (phase II part).

In this research, subjects received a single intravenous injection of 40 mg/m² talaporfin sodium. Four to 6 hours after administration of talaporfin sodium, the local residual/recurrent lesion was irradiated with 664-nm laser light (with a fluence of 50, 75, or 100 J/cm², and a fluence rate of 150 mW/cm²) with a semiconductor laser device. Lesions were endoscopically observed on the day following administration of talaporfin sodium and laser irradiation. If any residual lesion was detected, additional laser irradiation was performed.

All 19 subjects enrolled in the research (including 9 subjects enrolled in the phase I part) received talaporfin sodium (3 subjects in the 50 J/cm² cohort; 3 subjects in the 75 J/cm² cohort, and 13 subjects in the 100 J/cm² cohort), and were included in the safety analysis population. All 19 subjects who received talaporfin sodium-mediated PDT were included in the FAS.

Dose limiting toxicity did not occur in any cohort (3 subjects per cohort) in the phase I part. Therefore, the recommended fluence was determined to be 100 J/cm².

No adverse events resulted in death.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Clinical positioning

The Guidelines for the Diagnosis and Treatment of Carcinoma of the Esophagus, April 2012 version, edited by the Japan Esophageal Society (Kanehara & Co., Ltd.; 2012) (the Japanese guideline for the treatment of oesophageal carcinoma), state that PDT and other endoscopic treatment procedures are performed in patients with local residual/recurrent oesophageal carcinoma after CRT.

In contrast, PDT for local residual/recurrent oesophageal carcinoma after CRT or RT is not mentioned in the foreign guidelines, such as *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 10th edition* (PA, USA: Lippincott Williams & Wilkins; 2011), an internationally recognized textbook of oncology.

The applicant explained treatment modalities for local residual/recurrent oesophageal carcinoma after CRT or RT, and the clinical positioning of talaporfin sodium-mediated PDT among the treatment modalities.

The applicant's explanation:

While CRT and RT have been employed as treatment options for patients with oesophageal carcinoma who do not undergo surgical resection, the local residual tumor/recurrence rate in patients undergoing CRT or RT is as high as 34% to 40% (*N Engl J Med.* 1992;326:1593-8; *Int J Radiat Oncol Biol Phys.* 2003;57:425-33). Further, residual or recurrent lesions may cause dysphagia, malnutrition, airway stenosis, aspiration, chest pain, pneumonia due to fistula formation with adjacent organs, mediastinitis, pyothorax, major haemorrhage, and other conditions. Although no standard treatment has been established for patients with local residual/recurrent oesophageal carcinoma after CRT or RT, patients with tumor invasion limited to the muscularis propria have the following therapeutic options: surgical resection, endoscopic treatment (EMR or ESD), porfimer sodium-mediated PDT, and chemotherapy.

In patients with local residual/recurrent oesophageal carcinoma after CRT or RT who underwent porfimer sodium-mediate PDT, the rate of complete response (endoscopic or pathological disappearance of tumor) was 59.5% and the 5-year survival rate was 36.1%, with no particular safety concerns (*Endoscopy.* 2011;43:657-63). On the other hand, surgical resection in patients with local residual/recurrent oesophageal carcinoma after CRT or RT is reported to have a good prognosis if tumor removal is complete (*J Thorac Cardiovasc Surg.* 2009;137:49-54). Surgical resection, however, has safety problems, including a high incidence of postoperative complications and high treatment-related mortality. In patients with tumor invasion limited to the submucosa (among those with local residual/recurrent oesophageal carcinoma after CRT or RT) who underwent endoscopic treatment, the 5-year survival rate was 49%, with no particular safety concerns (*Gastrointest Endosc.* 2003;58:65-70; *Endoscopy.* 2008;40:717-21). In some patients, however, it is technically difficult to perform endoscopic treatment because of CRT- or RT-related ulcers or scars. [REDACTED]

The above findings suggest that, as with porfimer sodium-mediated PDT, talaporfin sodium-mediated PDT is a local treatment expected to alleviate or prevent symptoms accompanying the enlargement of local residual/recurrent lesions, and to improve the quality of life (QOL) in patients ineligible for surgical resection or endoscopic radical treatment.

PMDA accepted the applicant's explanation.

3.(i).B.(2) Efficacy

PMDA concluded that talaporfin sodium-mediated PDT is expected to be effective for the treatment of local residual/recurrent oesophageal carcinoma after CRT or RT, based on the following discussions.

Efficacy endpoint and evaluation results

The applicant explained the reason for selecting the efficacy endpoint and the evaluation results of Study KUTR-015-2, which was conducted in patients with local residual/recurrent oesophageal carcinoma after CRT or RT.

The applicant's explanation:

The purpose of talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma after CRT or RT is to control and eliminate local residual/recurrent lesions after CRT or RT, thereby alleviating and preventing symptoms including dysphagia, malnutrition, airway stenosis, aspiration, fistula formation, and chest pain, and improving QOL. An efficacy endpoint should therefore be a measure of tumor response (i.e., a measure representing the regression of local residual/recurrent lesion). Further, if complete response is not achieved and residual tumors are still present, these residual tumors may regrow, increasing the risk of developing the above symptoms; therefore, it was concluded that tumor complete response is of great importance, and the L-CR rate was selected as the primary endpoint.

According to the L-CR rate obtained in Study KUTR-015-2 [see "3.(i).A. Evaluation data. Japanese phase II study"], talaporfin sodium-mediated PDT is expected to be effective in patients with local residual/recurrent oesophageal carcinoma after CRT or RT.

PMDA's view:

Since Study KUTR-015-2 is an open-label, uncontrolled study, with no long-term treatment results, the study has limitations as a basis for assessing the efficacy of talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma after CRT or RT. However, PMDA concluded that talaporfin sodium-mediated PDT is expected to be effective in patients who fall within the target population of Study KUTR-015-2, based on the discussions in the section "3.(i).B.(1) Clinical positioning," taking into consideration the following points:

- Local residual/recurrent lesions after CRT or RT may cause conditions that could significantly deteriorate the patient's QOL. Such conditions include dysphagia, malnutrition, airway stenosis,

aspiration, fistula formation, and chest pain. Therefore, local control of the lesions has a certain clinical significance.

- The results of Study KUTR-015-2 suggest that talaporfin sodium-mediated PDT is expected to achieve L-CR at a certain level.

3.(i).B.(3) Safety [see “3.(ii) Adverse events reported in clinical studies” for the details of adverse events]

Close attention should be paid to oesophageal stenosis and oesophageal pain following the administration of talaporfin sodium to patients with local residual/recurrent oesophageal carcinoma after CRT or RT. Based on the discussion described in the following sections, PMDA concluded that talaporfin sodium-mediated PDT is tolerable, provided that these adverse events, as well as the adverse events observed in clinical studies of talaporfin sodium for the approved indications (i.e., early-stage lung cancer and primary malignant brain tumor) are carefully monitored in the same manner as in patients who receive treatment for the approved indications.

3.(i).B.(3).1 Safety profiles in patients with local residual/recurrent oesophageal carcinoma after CRT or RT

The applicant’s explanation on the safety of talaporfin sodium:

In the safety analysis population (26 subjects) of Study KUTR-015-2, adverse events occurred in 26 subjects (100%), Grade ≥ 3 adverse events in 6 subjects (23.1%), and serious adverse events in 1 subject (3.8%).

PMDA asked the applicant to explain the difference in safety profile between patients with local residual/recurrent oesophageal carcinoma after CRT or RT, and patients who receive treatment with talaporfin sodium for the approved indications, early-stage lung cancer or primary malignant brain tumor.

The applicant’s response:

Data from the following studies were analyzed: Study KUTR-015-2 in patients with local residual/recurrent oesophageal carcinoma after CRT or RT; a Japanese phase II study (Study ME2906-BT-1) in patients with primary malignant brain tumor; and another Japanese phase II study (Study 2906-2-1) in patients with early-stage lung cancer.

The incidence of the following adverse events was $\geq 10\%$ higher in subjects with local residual/recurrent oesophageal carcinoma than in subjects with early-stage lung cancer: oesophageal pain (53.8% and 0% in subjects with local residual/recurrent oesophageal carcinoma, and in subjects with early-stage lung cancer, respectively; the same applies hereinafter for the order of the patient groups), constipation (19.2% and 5.0%), aspartate aminotransferase (AST) increased (30.8% and 12.5%), blood albumin decreased (88.5% and 0%), blood potassium decreased (11.5% and 0%), blood potassium increased (30.8% and 0%), blood sodium decreased (26.9% and 2.5%), C-reactive protein increased (80.8% and 56.8%), neutrophil count increased (11.5% and 0%), lymphocyte count decreased (61.5% and 0%), and

protein total decreased (15.4% and 0%). A Grade ≥ 3 adverse event occurring at a $\geq 5\%$ higher incidence in subjects with local residual/recurrent oesophageal carcinoma than in subjects with early-stage lung cancer by was lymphocyte count decreased (15.4% and 0%, in the former and latter patient groups, respectively). Further, the incidence of the following adverse events was $\geq 10\%$ higher in subjects with local residual/recurrent oesophageal carcinoma than in subjects with primary malignant brain tumor: oesophageal pain (53.8% and 0% in subjects with local residual/recurrent oesophageal carcinoma, and in subjects with primary malignant brain tumor, respectively; the same applies hereinafter for the order of the subject groups), blood potassium increased (30.8% and 11.1%), neutrophil count increased (11.5% and 0%), and protein urine present (11.5% and 0%). There were no Grade ≥ 3 adverse events occurring at a $\geq 5\%$ higher incidence in subjects with local residual/recurrent oesophageal carcinoma than in subjects with primary malignant brain tumor.

The following adverse events occurred in ≥ 2 subjects with local residual/recurrent oesophageal carcinoma, but did not occur in any subjects with early-stage lung cancer or primary malignant brain tumor: oesophageal pain (14 subjects; 53.8%), neutrophil count increased (3 subjects; 11.5%), oesophageal stenosis (2 subjects; 7.7%), and lactescent serum (2 subjects; 7.7%). While a causal relationship to talaporfin sodium could not be ruled out for any of these events, all events were Grade 1 except for one event of Grade 2 oesophageal pain.

The majority of adverse events occurring at a higher incidence in subjects with local residual/recurrent oesophageal carcinoma than in subjects with early-stage lung cancer or primary malignant brain tumor had already been identified as requiring special caution at the time of the review of the application for the approved indications. Among adverse events occurring only in subjects with local residual/recurrent oesophageal carcinoma (in ≥ 2 subjects), oesophageal pain and oesophageal stenosis are considered to be due to a local reaction to talaporfin sodium-mediated PDT, occurring typically in patients with local residual/recurrent oesophageal carcinoma. However, all of these events were either Grade 1 or Grade 2. Oesophageal pain and oesophageal stenosis are thus unlikely to cause clinical problems. Neutrophil count increased and lactescent serum occurred only in subjects with local residual/recurrent oesophageal carcinoma; the reason for this is unclear, but all of these events were Grade 1 and resolved without treatment. Neutrophil count increased and lactescent serum are thus unlikely to cause clinical problems.

PMDA's view:

Attention should be paid to adverse events occurring at a higher incidence in subjects with local residual/recurrent oesophageal carcinoma compared with subjects with early-stage lung cancer or primary malignant brain tumor. The information on the occurrence of the adverse events in subjects with local residual/recurrent oesophageal carcinoma should be provided in an appropriate manner. A serious adverse event (hypotension) occurred in a subject in Study KUTR-015-2. The event was judged to be unrelated to talaporfin sodium, but information on the event should also be provided, because Study KUTR-015-2 was a single-arm study and therefore the relationship between the event and talaporfin sodium-mediated PDT has not been elucidated. Further, when performing talaporfin sodium-mediated

PDT in patients with local residual/recurrent oesophageal carcinoma after CRT or RT, extra attention should be paid to oesophageal pain and oesophageal stenosis, the adverse events occurring only in subjects with local residual/recurrent oesophageal carcinoma, but not in subjects with early-stage lung cancer or primary malignant brain tumor.

In addition to continuously paying attention to adverse events that have already been advised as requiring extra caution in patients who received treatment for the approved indications, the issues mentioned above need to be appropriately addressed. PMDA concluded that the tolerability of talaporfin sodium-mediated PDT is acceptable, provided that appropriate measures such as monitoring and management of adverse events are taken based on full understanding of the safety profiles of talaporfin sodium.

3.(i).B.(3).2) Oesophageal stenosis and oesophageal pain

The applicant's explanation on oesophageal stenosis and oesophageal pain associated with talaporfin sodium-mediated PDT:

In Study KUTR-015-2, oesophageal stenosis occurred in 2 of 26 subjects (7.7%), oesophageal pain in 14 of 26 subjects (53.8%), dysphagia in 2 of 26 subjects (7.7%), and odynophagia in 1 of 26 subjects (3.8%).

These adverse events occurring in Study KUTR-015-2 are summarized in the table below.

Adverse events associated with oesophageal stenosis and oesophageal pain

| Event | Grade | Circumferential spread | Lesion site* ¹ | Onset day* ² | Seriousness | Treatment | Causal relationship to talaporfin sodium | Outcome | Outcome day* ² |
|----------------------|-------|------------------------|---------------------------|-------------------------|----------------------------|---------------------------------|--|------------------------|---------------------------|
| Oesophageal stenosis | 1 | 1/4-1/2 | L | 28 | Non-serious | None | Related | Recovered | 58 |
| Oesophageal stenosis | 1 | <1/4 | M | 17 | Non-serious | None | Related | Recovered | 18 |
| Dysphagia | 2 | 1/4-1/2 | M | 4 | Non-serious | Endoscopic food residue removal | Related | Recovered | 6 |
| Dysphagia | 1 | 1/4-1/2 | L | 5 24 | Non-serious Non-serious | None None | Related Related | Recovered Recovered | 16 88 |
| Oesophageal pain | 2 | <1/4 | L | 1 | Non-serious | Analgesic | Related | Recovered | 5 |
| Oesophageal pain | 1 | 1/4-1/2 | L | 1 | Non-serious | None | Related | Recovered | 9 |
| Oesophageal pain | 1 | 1/4-1/2 | M | 1 | Non-serious | None | Related | Recovered | 2 |
| Oesophageal pain | 1 | <1/4 | M | 2 | Non-serious | Analgesic | Related | Recovered | 26 |
| Oesophageal pain | 1 | 1/4-1/2 | L | 2 | Non-serious | Analgesic | Related | Recovered | 21 |
| Oesophageal pain | 1 | <1/4 | L | 1 | Non-serious | None | Related | Recovered | 16 |
| Oesophageal pain | 1 | <1/4 | M | 1 | Non-serious | Analgesic | Related | Recovered | 3 |
| Oesophageal pain | 1 | 1/4-1/2 | M | 1 | Non-serious | Analgesic | Related | Recovered | 4 |
| Oesophageal pain | 1 | <1/4 | M | 7 | Non-serious | Analgesic | Related | Recovered | 15 |
| Oesophageal pain | 1 | <1/4 | L | 2 | Non-serious | Mucosal protectant | Related | Recovered | 8 |
| Oesophageal pain | 1 | <1/4 | M | 1 | Non-serious | Analgesic Mucosal protectant | Related | Recovered | 20 |
| Oesophageal pain | 1 | <1/4 | M | 1 | Non-serious | Analgesic | Related | Recovered | 13 |
| Oesophageal pain | 1 | <1/4 | U | 2 | Non-serious | Mucosal protectant | Related | Recovered | 23 |
| Oesophageal pain | 1 | <1/4 | M | 1 | Non-serious | Mucosal protectant | Related | Recovered | 29 |
| Odynophagia | 1 | 1/4-1/2 1/4-1/2 | U M | 3 | Non-serious | None | Related | Recovered | 44 |

*1 L (lower intrathoracic esophagus; >32 cm and ≤43 cm from the incisors), M (middle intrathoracic esophagus; >24 cm and ≤32 cm from the incisors), and U (upper intrathoracic esophagus; >18 cm and ≤24 cm from the incisors).

*2 Day 1 is defined as the day talaporfin sodium-mediated PDT was performed.

PMDA asked the applicant to explain the risk factors for developing oesophageal stenosis associated with talaporfin sodium-mediated PDT, the preventive and treatment measures, and the necessity of issuing an alert on the adverse event.

The applicant's response:

Following talaporfin sodium-mediated PDT, ulcers formed at the laser irradiated site or adjacent areas become scarred, resulting in oesophageal stenosis. Given this, a large circumferential spread is a risk factor for oesophageal stenosis. Endoscopy should therefore be performed to determine the presence or absence of oesophageal stenosis on a regular basis; further, patients with large circumferential spread should receive oral steroid or local steroid injection to prevent oesophageal stenosis following talaporfin sodium-mediated PDT. In the event of oesophageal stenosis, endoscopic balloon dilation is recommended. In Study KUTR-015-2, endoscopic balloon dilation was performed in 1 of 26 subjects (3.8%). However, if ulcers caused by talaporfin sodium-mediated PDT extend beyond the muscularis propria, endoscopic balloon dilation should be avoided because it may cause oesophageal perforation, and other appropriate measures (e.g., short-term fasting) should be taken. In Study KUTR-015-2, patients were carefully monitored after PDT to determine the presence or absence of oesophageal stenosis and to regularly examine the condition of ulcers caused by PDT, and received appropriate treatments as necessary. In the study, adverse events such as oesophageal stenosis could be managed through these measures; accordingly, the information on these measures should be provided to healthcare professionals.

PMDA's view:

Oesophageal stenosis and oesophageal pain that occurred in Study KUTR-015-2 were able to be managed through the following measures: regular endoscopy; endoscopic balloon dilation and other measures for oesophageal stenosis or dysphagia; and administration of an analgesic for oesophageal pain. Therefore, oesophageal stenosis and oesophageal pain associated with talaporfin sodium-mediated PDT are generally manageable, provided that endoscopy is performed on a regular basis after talaporfin sodium-mediated PDT, and appropriate measures are taken in the event of these adverse events, in the same manner as they were performed in the clinical study.

In addition to the paucity of patient data to assess the safety of talaporfin sodium-mediated PDT, the applicant explained that (a) patients with lesions in which the circumferential spread is more than half of the luminal circumference were excluded from Study KUTR-015-2; (b) 1 subject underwent endoscopic balloon dilation to treat oesophageal stenosis,* which was not reported as an adverse event; (c) benefits of preventive measures for oesophageal stenosis have not been clearly demonstrated; and (d) if performed in patients with deep ulcers, endoscopic balloon dilation may cause oesophageal perforation, which could have fatal consequences. Based on the above, PMDA considers that the package insert should provide information on (1) patients enrolled in the clinical study, (2) the details of regular endoscopic monitoring methods used in the clinical study, (3) the preventive measures actually taken against oesophageal stenosis, and (4) the incidence of oesophageal stenosis and oesophageal pain. PMDA also considers that the applicant should appropriately advise healthcare professionals to take appropriate measures in the event of oesophageal stenosis or oesophageal pain.

* Endoscopic balloon dilation and local steroid injection were performed 84 days and 97 days after talaporfin sodium-mediated PDT; and endoscopic balloon dilation was performed 119 days and 36 weeks after talaporfin sodium-mediated PDT.

3.(i).B.(3).3) Photosensitivity

The applicant's explanation on the light protection methods used in Study KUTR-015-2 for managing or preventing photosensitivity reactions in patients:

Since talaporfin sodium has been known to induce photosensitivity, the protocol of Study KUTR-015-2 specified that subjects should wear sunglasses for 3 days following administration of talaporfin sodium, stay in a room in which illuminance was controlled at ≤ 500 lux using blackout curtains or other light shading measures for 2 weeks following administration of talaporfin sodium, and preferably avoid direct sunlight for 4 weeks following administration of talaporfin sodium.

The results of KUTR-015-2 showed that 1 adverse event (purpura) classified as skin and subcutaneous tissue disorders (MedDRA System Organ Class [SOC]) occurred in 1 of 26 subjects (3.8%) 1 day after administration; however, the possibility of photosensitivity was ruled out for this event.

In the initial approval of talaporfin sodium, the timing of conducting a skin photosensitivity test for determining whether light protection measures can be discontinued, was defined as "2 weeks after administration of talaporfin sodium." In the current application, however, the applicant proposed to change the timing to "1 week after administration of talaporfin sodium." PMDA asked the applicant to explain the appropriateness of the change.

The applicant's response:

Currently, the package insert for the approved indications (early-stage lung cancer and primary malignant brain tumor) specifies that patients should be protected from light (≤ 500 lux) for 2 weeks after administration of talaporfin sodium. This measure was based on the following findings: (1) In Study 2906-2-1, 28 of 33 subjects (84.8%) showed no photosensitivity reactions in skin photosensitivity tests conducted by 2 weeks post-dose. (2) In Study ME2906-BT-1, 21 of 27 subjects (77.8%) showed the absence or disappearance of photosensitivity reactions in skin photosensitivity tests conducted by 8 days post-dose, and 27 of 27 subjects (100%) by 15 days post-dose. (3) In Study ME2906-BT-1, however, after discontinuing the light protection measures, adverse events classified as skin and subcutaneous tissue disorders (SOC) occurred in 13 of 27 subjects (48.1%), and a causal relationship to talaporfin sodium could not be ruled out in 1 patient with rash.

Skin photosensitivity tests* conducted in Study KUTR-015-2 showed that 69.2% (18 of 26) of subjects had a score of 0 at 7 days after administration of talaporfin sodium and 100% (26 of 26) of subjects at 15 days after administration of talaporfin sodium. No adverse events in the skin and subcutaneous tissue disorders (SOC) occurred after the light protection measures were discontinued.

* Photosensitivity reactions such as erythema were evaluated according to the criteria shown in the table below by exposing the dorsum of the hand or other area of skin of patients to direct sunlight for 5 minutes between 11 a.m. and 2 p.m., prior to administration of talaporfin sodium, 5 to 9 days, 12 to 16 days, 19 to 23 days, and 26 to 30 days after administration of talaporfin sodium, and on the day of study discontinuation.

| Score | Criteria |
|-------|------------------------------|
| 0 | No change |
| 1 | Slightly noticeable erythema |
| 2 | Clear erythema |
| 3 | Strong erythema or oedema |

Based on the above discussion, the applicant considered it appropriate to change the timing of skin photosensitivity testing to 1 week after administration of talaporfin sodium.

PMDA's view:

No patients experienced skin disorders after the light protection measures were discontinued in Study KUTR-015-2. However, in view of the issues listed below, patients receiving talaporfin sodium for the treatment of local residual/recurrent oesophageal carcinoma should be protected from light, and these patients and healthcare professionals should be cautioned against skin disorders appropriately, as with patients receiving the treatment for the approved indications. The period of light protection in patients with local residual/recurrent oesophageal carcinoma should be the same as that in patients receiving treatment for the approved indications, in order to ensure a careful light protection.

- Talaporfin sodium is a photosensitizer, and the proposed dosage and route of administration for the current application are the same as those for the approved indications.
- In Study ME2906-BT-1, 1 subject experienced rash after discontinuing the light protection measures, and a causal relationship to talaporfin sodium could not be ruled out for this event.

3.(i).B.(3).4 Safety in patients who received additional laser irradiation

The applicant's explanation on the safety in patients who received additional laser irradiation:

In Study KUTR-015-2, additional laser irradiation was performed in 16 of 26 subjects (61.5%). Adverse events occurred in all 26 subjects, regardless of additional laser irradiation. Grade ≥ 3 adverse events occurred in 18.8% (3 of 16) of subjects receiving additional laser irradiation, and in 30.0% (3 of 10) of subjects not receiving additional laser irradiation.

The incidence of the following adverse events was $\geq 10\%$ higher in subjects who underwent laser irradiation than in those who did not: AST increased (37.5%, and 20.0% in subjects with additional laser irradiation, and in subjects with no additional laser irradiation, respectively; the same applies hereinafter in this paragraph for the order of subject groups); blood potassium increased (37.5% and 20.0%), haemoglobin decreased (31.3% and 10.0%). The following adverse events occurred in ≥ 2 subjects who underwent additional laser irradiation, but did not occur in any of the subjects who did not undergo additional laser irradiation: blood alkaline phosphatase increased (3 subjects; 18.8%), dysphagia, nausea, and neutrophil count decreased (2 subjects each; 12.5%).

All events of dysphagia and nausea were Grade ≤ 2 . All laboratory test abnormalities were Grade 1 and resolved without any treatment, except for Grade 3 neutrophil count decreased in 1 patient. These events

are thus unlikely to pose any clinical problems. Accordingly, there are no adverse events requiring particular attention in patients receiving additional laser irradiation.

PMDA's view:

There were adverse events that occurred at a higher incidence in subjects who underwent additional laser irradiation than in subjects who did not, or that occurred only in subjects who underwent additional laser irradiation, but not in subjects who did not. Therefore, it is necessary to pay close attention to these adverse events in patients undergoing additional laser irradiation, and to provide a caution on the status of occurrence of the adverse events in an appropriate manner.

3.(i).B.(3).5 Safety in patients with aortic invasion (T4) diagnosed by computed tomography (CT) prior to CRT or RT

The applicant's explanation on the safety in patients with a diagnosis of aortic invasion (T4):

There was a report that a patient who had been diagnosed with aortic invasion (T4) by CT prior to CRT or RT experienced an aorto-oesophageal fistula following porfimer sodium-mediated PDT, resulting in death. Therefore, patients with aortic invasion (T4) were excluded from Study KUTR-015-2 under the eligibility criteria. Talaporfin sodium-mediated PDT may pose a risk of serious adverse events (e.g., aorto-oesophageal fistula and oesophageal perforation) in patients with aortic invasion (T4). As there are no effective measures to reduce the risk, talaporfin sodium-mediated PDT should be contraindicated in patients with aortic invasion (T4).

PMDA accepted the applicant's explanation.

3.(i).B.(4) Indications

The proposed indication for talaporfin sodium was "local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy."

Based on the discussions in the above sections [see "3.(i).B.(1) Clinical positioning," "3.(i).B.(2) Efficacy," and "3.(i).B.(3) Safety"] and in the following sections, PMDA concluded that the proposed indication, "local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy," is acceptable, provided that the "Precautions for indications" section includes statements to the following effect:

- Radical treatment (e.g., surgical resection, endoscopic treatment [EMR or ESD]) should be prioritized over talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma who are eligible for such radical treatment.
- The eligibility of a patient with local residual/recurrent oesophageal carcinoma for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the "Clinical studies" section for the disease stages and other information of patients enrolled in the study, and becoming fully acquainted with the efficacy and safety of talaporfin sodium.

- The efficacy and safety of talaporfin sodium-mediated PDT have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the following criteria:
 - (a) Lesions classified as T3 or T4, in terms of depth of invasion
 - (b) Lesions with a major axis of >3 cm
 - (c) Lesions in which the circumferential spread is more than half of the luminal circumference
 - (d) Lesions extending to the cervical esophagus

Discussion on eligible patients for talaporfin sodium-mediated PDT

In the current application, the following cautionary statements are proposed in the “Precautions for indications” section:

- The efficacy and safety have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the criteria (a) to (d) (see below). Therefore, in order to determine whether a patient is eligible for treatment with talaporfin sodium, testing such as endoscopic ultrasonography should be conducted to determine the depth of invasion, size, and other conditions of the tumor. Talaporfin sodium-mediated PDT should be performed only after evaluating the risks and benefits of the treatment based on these results.
 - (a) Lesions classified as T3 or T4, in terms of depth of invasion
 - (b) Lesions with a major axis of >3 cm
 - (c) Lesions in which the circumferential spread is more than half of the luminal circumference
 - (d) Lesions extending to the cervical esophagus

Patients eligible for surgical resection or endoscopic treatment (EMR or ESD) were excluded from Study KUTR-015-2. PMDA asked the applicant to discuss the appropriateness of talaporfin sodium-mediated PDT in such patients.

The applicant’s response:

There are no study results showing the efficacy and safety of talaporfin sodium-mediated PDT in such patients. Surgical resection and endoscopic treatment (EMR or ESD) should therefore be prioritized over talaporfin sodium-mediated PDT in such patients. This information should be provided as a cautionary statement in the “Precautions for indications” section of the package insert.

PMDA’s view:

The applicant’s explanation is generally acceptable. Since Study KUTR-015-2 excluded patients with distant metastasis or metastases to lymph nodes, for which systemic chemotherapy is indicated, the applicant should provide information on the disease stages of patients enrolled in Study KUTR-015-2 (in the “Clinical Studies” section of the package insert) and add the following cautionary statement to the “Precautions for indications” section of the package insert:

- The eligibility of a patient for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the “Clinical studies” section for the disease stages and other information of

patients enrolled in the study, and becoming fully acquainted with the efficacy and safety of talaporfin sodium.

3.(i).B.(5) Dosage and administration

The proposed dosage and administration for talaporfin sodium was as follows: “The dosage is 40 mg/m² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection.”

Based on the discussions in the following sections, PMDA concluded that the proposed dosage and administration for talaporfin sodium were acceptable, and that a statement to the following effect should be included in the “Precautions for dosage and administration” section:

- In patients with local residual/recurrent oesophageal carcinoma, the irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous administration of talaporfin sodium.

3.(i).B.(5).1 Dosage of talaporfin sodium

The applicant’s explanation on the dosage of talaporfin sodium:

In Study KUTR-015-2, talaporfin sodium was administered at the same dosage recommended for the approved indications (early-stage lung cancer and primary malignant brain tumor), and the efficacy and safety of the dosage were demonstrated. Therefore, 40 mg/m² (the same dosage recommended for the approved indications) was selected for patients with local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy. No other dose levels have been studied.

PMDA’s view:

It is unknown whether the dosage selected in Study KUTR-015-2 is optimal for patients with local residual/recurrent oesophageal carcinoma, because no other dose levels have been studied. However, given that Study KUTR-015-2 demonstrated a certain degree of efficacy and safety of talaporfin sodium, the proposed dosage and administration is acceptable.

3.(i).B.(5).2 Interval between talaporfin sodium administration and laser irradiation, additional laser irradiation, and fluence

In the current application, the proposed timing of laser irradiation was “between 4 and 6 hours after intravenous injection,” namely, a 4- to 6-hour interval between administration of talaporfin sodium and laser irradiation (as presented in the proposed “Dosage and administration” section). A cautionary statement regarding additional laser irradiation (see below) was included in the proposed “Precautions for dosage and administration” section. The proposed fluence of laser light was 100 J/cm² (as presented in the proposed package insert).

[Precautions for dosage and administration]

- In patients with local residual/recurrent oesophageal carcinoma, the irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous administration of talaporfin sodium.

The applicant explained the grounds for setting the time of laser irradiation, additional laser irradiation, and fluence in Study KUTR-015-2, and the appropriateness of the above-mentioned cautionary statement regarding these matters.

The applicant's explanation:

The interval between administration of talaporfin sodium and laser irradiation in Study KUTR-015-2 was determined based on the results of a foreign phase I study conducted in patients with superficial malignant tumors for the assessment of the safety, tolerability, and other aspects of talaporfin sodium-mediated PDT. The interval used in Study KUTR-015-2 was identical to that used in a Japanese phase I study (in patients with early-stage lung cancer) and Study 2906-2-1.

The movement of irradiation site caused by respiratory movement, heartbeat, peristalsis, spasm, and other reasons may result in insufficient laser light irradiation. Lesions were therefore examined endoscopically on the day following laser irradiation, and if any residual lesion was detected, additional laser irradiation was performed [see "3.(i).A. Evaluation data. Japanese phase II study"].

The fluence was selected based on the occurrence of dose limiting toxicity in the clinical research [see "3.(i).A. Reference data. Japanese clinical research"].

Study KUTR-015-2, conducted under the conditions as described above, demonstrated that talaporfin sodium-mediated PDT has a certain degree of efficacy and safety in patients with local residual/recurrent oesophageal carcinoma after CRT or RT [see "3.(i).B.(2) Efficacy" and "3.(i).B.(3).4) Safety in patients who received additional laser irradiation"]; therefore, it is appropriate to provide a cautionary statement regarding the interval between administration of talaporfin sodium and laser irradiation, additional laser irradiation, and fluence in the "Dosage and administration" and "Precautions for dosage and administration" sections.

PMDA's view:

It is unknown whether the benefit-risk balance of talaporfin sodium-mediated PDT can be optimized by "the interval between administration of talaporfin sodium and laser irradiation," "the conditions for additional laser irradiation," and "the fluence" used in Study KUTR-015-2. However, given that Study KUTR-015-2 demonstrated a certain degree of efficacy and safety of talaporfin sodium-mediated PDT, PMDA accepted the applicant's explanation on the provision of a cautionary statement regarding the

interval between administration of talaporfin sodium and laser irradiation, conditions for additional laser irradiation, and fluence.

3.(i).B.(6) Post-marketing investigations

3.(i).B.(6).1) Post-marketing surveillance of talaporfin sodium

The applicant's explanation on the post-marketing surveillance plan:

A post-marketing surveillance will be conducted using a central registration method in patients with local residual/recurrent oesophageal carcinoma who receive talaporfin sodium, mainly to assess the safety of talaporfin sodium-mediated PDT in postmarketing clinical settings.

Among important identified risks for talaporfin sodium, photosensitivity and hepatic dysfunction will be excluded from the priority survey items for the post-marketing surveillance because of the absence of serious cases in Study KUTR-015-2. Dyspnoea, another important identified risk, will also be excluded from the priority survey items because it is a typical event in early-stage lung cancer.

The target sample size was determined to be 100 patients based on the incidence of each adverse reaction reported in Study KUTR-015-2.

The follow-up period was set at 30 days because in Study KUTR-015-2 all adverse events had developed by 30 days after PDT.

PMDA's view:

The use-results survey in Japanese patients with early-stage lung cancer (the approved indication) who underwent talaporfin sodium-mediated PDT has already been completed. A certain amount of safety data on Japanese patients have thus already been collected. However, another use-results survey should be conducted to assess the safety and other aspects of talaporfin sodium-mediated PDT in the Japanese clinical settings, because Study KUTR-015-2 enrolled only 26 patients and reported some adverse events that had not been reported by clinical studies for the approved indications, early-stage lung cancer or primary malignant brain tumor [see "3.(i).B.(3) Safety"].

The post-marketing surveillance should include oesophageal stenosis and oesophageal perforation as the priority survey items: Oesophageal stenosis was first reported in Study KUTR-015-2. Oesophageal perforation was not reported in Study KUTR-015-2, but has been reported in a patient undergoing PDT with a similar drug; attention should therefore be paid to oesophageal perforation in patients undergoing talaporfin sodium-mediated PDT.

The follow-up period should be at least 3 months after PDT, because (1) in Study KUTR-015-2, a patient underwent endoscopic dilation of the esophagus and local steroid injection to treat oesophageal stenosis at 84 days after talaporfin sodium-mediated PDT, and (2) there is a report of oesophageal perforation

that occurred approximately 2 months after PDT with a similar drug. The target sample size proposed by the applicant is acceptable.

3.(i).B.(6).2 Proper treatment with talaporfin sodium-mediated PDT

The applicant's explanation on the measures for proper treatment with talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma in postmarketing settings:

In cooperation with the relevant academic societies, the applicant will prepare guidelines on treatment with talaporfin sodium-mediated PDT, develop training programs, and host training sessions. The guidelines, training programs, and training sessions will be provided to physicians who perform talaporfin sodium-mediated PDT, to ensure that they are familiar with (a) the eligibility for talaporfin sodium-mediated PDT; (b) the appropriate environment and conditions for treatment; and (c) how to use the semiconductor laser device for PDT.

PMDA accepted the applicant's explanation.

3.(ii) Adverse events reported in clinical studies

The data on deaths in the submitted clinical studies are presented in the "3.(i) Summary of clinical efficacy and safety." The following sections summarize other main adverse events observed in the studies.

3.(ii).(1) Clinical research (Study KUTR-015-1)

Adverse events occurred in 3 of 3 subjects (100%) irradiated with a fluence of 50 J/cm² (level 1), 2 of 3 subjects (66.7%) irradiated with 75 J/cm² (level 2), and 9 of 13 subjects (69.2%) irradiated with 100 J/cm² (level 3). Adverse events for which a causal relationship to talaporfin sodium could not be ruled out occurred in 1 of 3 subjects (33.3%) in the 50 J/cm² (level 1) group, 2 of 3 subjects (66.7%) in the 75 J/cm² (level 2) group, and 8 of 13 subjects (61.5%) in the 100 J/cm² (level 3) group.

The table below shows adverse events occurring with an incidence of $\geq 10\%$ in at least 1 group.

Adverse events occurring with an incidence of $\geq 10\%$ in at least 1 group

| System Organ Class Preferred Term (MedDRA/J ver 17.0) | Number of subjects (%) | | | | | |
|---|---|----------------|---|----------------|---|----------------|
| | 50 J/cm ² group (3 subjects) | | 75 J/cm ² group (3 subjects) | | 100 J/cm ² group (13 subjects) | |
| | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 |
| Adverse events total | 3 (100%) | 0 | 2 (66.7%) | 0 | 9 (69.2%) | 0 |
| Gastrointestinal disorders | | | | | | |
| Oesophageal pain | 1 (33.3%) | 0 | 2 (66.7%) | 0 | 6 (46.2%) | 0 |
| Dysphagia | 1 (33.3%) | 0 | 0 | 0 | 4 (30.8%) | 0 |
| General disorders and administration site conditions | | | | | | |
| Pyrexia | 0 | 0 | 1 (33.3%) | 0 | 0 | 0 |
| Investigations | | | | | | |
| White blood cell count decreased | 1 (33.3%) | 0 | 0 | 0 | 0 | 0 |
| Blood sodium decreased | 1 (33.3%) | 0 | 0 | 0 | 0 | 0 |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 0 | 2 (15.4%) | 0 |
| Skin and subcutaneous tissue disorders | | | | | | |
| Dry skin | 1 (33.3%) | 0 | 0 | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | | | | |
| Anaemia | 0 | 0 | 0 | 0 | 2 (15.4%) | 0 |

There were no serious adverse events, or adverse events that led to treatment discontinuation of talaporfin sodium in any of the groups.

3.(ii).(2) Japanese phase II study (Study KUTR-015-2)

Adverse events occurred in 26 of 26 subjects (100%). All 26 subjects (100%) experienced an adverse event for which a causal relationship to talaporfin sodium could not be ruled out.

The table below shows adverse events with an incidence of $\geq 10\%$.

| Adverse events with an incidence of $\geq 10\%$ | | |
|---|------------------------|----------------|
| System Organ Class Preferred Term (MedDRA/J ver 17.0) | Number of subjects (%) | |
| | 26 subjects | |
| | All Grades | Grade ≥ 3 |
| Adverse events total | 26 (100%) | 6 (23.1%) |
| Investigations | | |
| Blood albumin decreased | 23 (88.5%) | 0 |
| C-reactive protein increased | 21 (80.8%) | 0 |
| Lymphocyte count decreased | 16 (61.5%) | 4 (15.4%) |
| Aspartate aminotransferase increased | 8 (30.8%) | 0 |
| Blood potassium increased | 8 (30.8%) | 0 |
| Blood sodium decreased | 7 (26.9%) | 1 (3.8%) |
| Alanine aminotransferase increased | 6 (23.1%) | 0 |
| Haemoglobin decreased | 6 (23.1%) | 0 |
| Protein total decreased | 4 (15.4%) | 0 |
| White blood cell count decreased | 4 (15.4%) | 0 |
| Blood potassium decreased | 3 (11.5%) | 0 |
| Gamma-glutamyltransferase increased | 3 (11.5%) | 0 |
| Neutrophil count increased | 3 (11.5%) | 0 |
| Protein urine present | 3 (11.5%) | 0 |
| Blood alkaline phosphatase increased | 3 (11.5%) | 0 |
| Gastrointestinal disorders | | |
| Oesophageal pain | 14 (53.8%) | 0 |
| Constipation | 5 (19.2%) | 0 |
| General disorders and administration site conditions | | |
| Pyrexia | 8 (30.8%) | 0 |

A serious adverse event (hypotension) occurred in 1 of 26 subjects (3.8%). A causal relationship to the study drug was ruled out for the event.

There were no adverse events that led to treatment discontinuation of talaporfin sodium.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2-01). The results showed satisfactory overall GCP compliance in the conduct of clinical studies, and PMDA therefore concluded that there should be no problem in conducting a regulatory review based on the submitted application documents. However, the following issues were found at some trial sites, albeit with no major impact on the overall

study evaluation. The issues were identified as an area for improvement and notified to the head of the medical institutions.

Area for improvement

Clinical trial sites

- A clinical trial-related task (upper gastrointestinal endoscopy examination) was performed by a physician whose name is not listed in the task assignment list prepared by the investigator.
- A clinical trial-related examination (skin photosensitivity testing) was performed before informed consent had been obtained.

IV. Overall Evaluation

Based on the submitted data, the efficacy of the product in the treatment of local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy has been demonstrated, and its safety is acceptable in view of its observed benefits. Talaporfin sodium is a clinically meaningful treatment option for local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy. Indications, dosage and administration, post-marketing investigations, and other issues will be further discussed in the Expert Discussion.

Talaporfin sodium may be approved if the product is considered to have no particular problems based on comments from the Expert Discussion.

Review Report (2)

April 10, 2015

I. Product Submitted for Registration

| | |
|------------------------|----------------------------------|
| [Brand name] | Laserphyrin 100 mg for Injection |
| [Non-proprietary name] | Talaporfin Sodium |
| [Applicant] | Meiji Seika Pharma Co., Ltd. |
| [Date of application] | September 22, 2014 |

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the “Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

(1) Clinical positioning and efficacy

PMDA’s conclusion:

Study KUTR-015-2 (a Japanese phase II study in patients with local residual/recurrent oesophageal carcinoma after chemoradiotherapy [CRT] or radiotherapy [RT]) has limitations as a basis for evaluating the efficacy of talaporfin sodium-mediated photodynamic therapy (PDT), because it was an open-label, uncontrolled study and no long-term results have been obtained from the study. However, the discussions in “II.3.(i).B.(1) Clinical positioning” of Review Report (1) have shown that talaporfin sodium-mediated PDT is a new local treatment option for patients with local residual/recurrent oesophageal carcinoma after CRT or RT. Further, the local complete response rate in Study KUTR-015-2 was 88.5% [95% confidence interval: 69.8%, 97.6%]. PMDA has thus concluded that talaporfin sodium-mediated PDT is expected to be effective in the treatment of local residual/recurrent oesophageal carcinoma after CRT or RT.

This conclusion was supported by the expert advisors at the Expert Discussion.

(2) Safety

PMDA’s conclusion:

According to the discussion in “II.3.(i).B.(3) Safety” of Review Report (1), oesophageal stenosis and oesophageal pain were identified as adverse events requiring extra caution when talaporfin sodium-mediated PDT is performed in patients with local residual/recurrent oesophageal carcinoma after CRT or RT. Nevertheless, PMDA has concluded that talaporfin sodium-mediated PDT is tolerable, provided that these patients are carefully monitored for these adverse events, as well as for adverse events

observed in clinical studies for the approved indications (early-stage lung cancer or primary malignant brain tumor), in the same manner as patients receiving treatment for the approved indications.

Talaporfin sodium-mediated PDT may cause serious adverse events (e.g., aorto-oesophageal fistula) in patients with aortic invasion (T4) diagnosed by computed tomography (CT) prior to CRT or RT. PMDA therefore concluded that talaporfin sodium-mediated PDT should be contraindicated in such patients.

This conclusion was supported by the expert advisors at the Expert Discussion. The following comments were made by an expert advisor:

- Patients with tracheal or bronchial invasion diagnosed by CT prior to CRT or RT have an increased risk of oesophageal perforation associated with talaporfin sodium-mediated PDT. The applicant should issue a cautionary statement regarding the risk.

PMDA asked the applicant to explain the safety of talaporfin sodium-mediated PDT in patients with tumor invasion to the adjacent organs as diagnosed by CT prior to CRT or RT.

The applicant's response:

The safety of talaporfin sodium-mediated PDT has not been established in patients with tumor invasion to the adjacent organs as diagnosed by CT prior to CRT or RT, because such patients were not enrolled in Study KUTR-015-2. In such patients, since tissues around the esophagus become fragile after CRT or RT, talaporfin sodium-mediated PDT may cause tissue damage extending beyond the oesophageal wall, possibly resulting in oesophageal perforation.

PMDA's view:

Patients with tracheal or bronchial invasion diagnosed by CT prior to CRT or RT may have an increased risk of oesophageal perforation associated with talaporfin sodium-mediated PDT. Therefore, using the package insert or other relevant materials, the applicant should appropriately advise healthcare professionals to determine the eligibility of a patient for talaporfin sodium-mediated PDT according to the condition of the tumor on CT performed prior to CRT or RT. It is also necessary to collect information on the condition of tumors on CT performed prior to CRT or RT in patients who presented with oesophageal perforation, an adverse event that should be selected as a priority survey item for the post-marketing surveillance [see "II.3.(i).B.(6) Post-marketing investigations"]. New findings obtained from the surveillance should be provided to healthcare professionals in an appropriate manner.

PMDA instructed the applicant to take appropriate measures on the above issues. The applicant agreed.

(3) Indications

Based on the discussions in the "II.3.(i).B.(1) Clinical positioning" and "II.3.(i).B.(4) Indications" of Review Report (1), PMDA concluded that the proposed indication for talaporfin sodium, "local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy," is appropriate,

provided that the following cautionary statements are included in the “Precaution for indications” section:

[Precautions for indications]

- Radical treatment (e.g., surgical resection, endoscopic treatment [EMR or ESD]) should be prioritized over talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma who are eligible for such radical treatment.
- The eligibility of a patient for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the “Clinical studies” section for the histological types of cancers and other information of patients enrolled in the clinical study, and becoming fully acquainted with the efficacy and safety of talaporfin sodium.
- The efficacy and safety of talaporfin sodium-mediated PDT have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the following criteria:
 - (a) Lesions classified as T3 or T4, in terms of depth of invasion
 - (b) Lesions with a major axis of >3 cm
 - (c) Lesions in which the circumferential spread is more than half of the luminal circumference
 - (d) Lesions extending to the cervical esophagus

This conclusion was supported by the expert advisors at the Expert Discussion.

(4) Dosage and administration

After the discussion in the “II.3.(i).B.(5) Dosage and administration” of Review Report (1), PMDA concluded that the “Dosage and administration” and “Precautions for dosage and administration” section should be as follows:

[Dosage and administration]

The usual adult dosage is 40 mg/m² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection.

[Precautions for dosage and administration]

- The irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous administration of talaporfin sodium.

This conclusion was supported by the expert advisors at the Expert Discussion.

(5) Post-marketing investigations and risk management plan (draft)

After the discussion presented in “II.3.(i).B.(6) Post-marketing investigations” of Review Report (1), PMDA concluded that a post marketing surveillance should be conducted to assess the safety and other aspects of talaporfin sodium-mediated PDT in clinical settings, and safety information collected should

be provided to healthcare professionals in an appropriate manner, because Study KUTR-015-2 enrolled only a limited number of patients and reported some adverse events that had not been reported by the clinical studies conducted for the approved indications.

PMDA's conclusion regarding the plan for the post-marketing surveillance:

- (a) Oesophageal stenosis and oesophageal perforation should be included in the priority survey items: Oesophageal stenosis was first reported in Study KUTR-015-2. Oesophageal perforation requires caution because it was reported in a patient undergoing PDT with a similar drug, although it was not reported by Study KUTR-015-2.
- (b) The proposed target sample size for the surveillance (100 patients) is acceptable.
- (c) The follow-up period should be 3 months after PDT, because (1) in Study KUTR-015-2, a patient underwent endoscopic dilation of the esophagus and local steroid injection to treat oesophageal stenosis at 84 days after talaporfin sodium-mediated PDT, and (2) the reported case of oesophageal perforation occurred approximately 2 months after PDT with a similar drug.

Further, in order to perform talaporfin sodium-mediated PDT properly, it is essential for a physician to gain the necessary knowledge and skills required for the procedure. Therefore, after market launch, appropriate measures should be taken to ensure that talaporfin sodium will be administered only under the supervision of a physician who has undergone a training session on talaporfin sodium-mediated PDT, and has sufficient knowledge and experience in photodynamic therapy.

This conclusion was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to take appropriate measures on the above issues. The applicant agreed.

Based on the above discussion, PMDA concluded that the applicant should establish the safety and efficacy specification in the risk management plan (draft), and implement additional pharmacovigilance actions and risk minimization actions, as shown in the table below.

Safety and efficacy specification for the risk management plan (draft)

| | | |
|---|--|-------------------------------|
| Safety specification | | |
| Important identified risks | Important potential risks | Important missing information |
| <ul style="list-style-type: none"> • Photosensitivity • Hepatic dysfunction • Dyspnoea (early-stage lung cancer) • Oesophageal stenosis (local residual/recurrent oesophageal carcinoma after CRT or RT) | <ul style="list-style-type: none"> • Oesophageal perforation (local residual/recurrent oesophageal carcinoma after CRT or RT) | None |
| Efficacy specification | | |
| <ul style="list-style-type: none"> • Efficacy in patients with primary malignant brain tumor in clinical settings (use-results survey) • Efficacy in patients with local residual/recurrent oesophageal carcinoma after CRT or RT in clinical settings (use-results survey) | | |

Summary of additional pharmacovigilance and risk minimization actions for the risk management plan (draft)

| | |
|---|--|
| Additional pharmacovigilance actions | Additional risk minimization actions |
| <ul style="list-style-type: none"> • <u>Early post-marketing phase vigilance (local residual/recurrent oesophageal carcinoma after CRT or RT)</u> • Use-results survey for primary malignant brain tumor • <u>Use-results survey for local residual/recurrent oesophageal carcinoma after CRT or RT (see the table below for the outline of use-results survey plan [draft])</u> | <ul style="list-style-type: none"> • <u>Information provision by implementing early post-marketing phase vigilance (local residual/recurrent oesophageal carcinoma after CRT or RT)</u> • <u>Specifying use conditions</u> |

Items underlined are activities planned for the new indication.

Outline of use-results survey plan (draft)

| | |
|---------------------|---|
| Objective | To assess the safety and other aspects of talaporfin sodium under actual use conditions |
| Survey method | Central registration method |
| Target patients | Patients with local residual/recurrent oesophageal carcinoma after CRT or RT, who received talaporfin sodium |
| Follow-up period | For 3 months after PDT |
| Planned sample size | 100 patients |
| Main survey items | Priority survey items: oesophageal stenosis and oesophageal perforation Main survey items other than above include patient characteristics, status of treatment with talaporfin sodium, concomitant medications and therapies, adverse events (including changes in laboratory values) |

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indications, and dosage and administration as shown below, with the conditions for approval, provided that cautions and information for proper use are provided in an appropriate manner through the package insert or other relevant measures after the market launch, and that the product will be administered properly only under the supervision of a physician with sufficient knowledge and experience in photodynamic therapy. Since talaporfin sodium is designated as an orphan drug for the additional indication proposed in this application, the re-examination period for this new indication should be 10 years.

[Indications] (Words underlined are additions.)

- (1) Early-stage lung cancer (Stage 0 or I) treatable with laser irradiation in patients ineligible for other radical interventions including surgical resection, or in patients who require the preservation of pulmonary function but cannot receive other treatments. The entire tumor must be observable endoscopically.
- (2) Primary malignant brain tumor (only in patients who undergo resection of brain tumor)

(3) Local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy

[Dosage and administration] (Words underlined are additions.)

(1) Early-stage lung cancer, and local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy

The usual adult dosage is 40 mg/m² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection.

(2) Primary malignant brain tumor

The usual adult dosage is 40 mg/m² of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 22 and 26 hours after intravenous injection.

[Conditions for approval]

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Take necessary measures to ensure that the product is administered only by physicians with sufficient knowledge and experience in photodynamic therapy who have undergone a training session on photodynamic therapy with the product.

[Contraindications] (Words underlined are additions.)

1. Patients with known hypersensitivity to any ingredient of the product
2. Patients with porphyria (The symptoms may be worsened.)
3. Patients with lung cancer invading beyond the bronchial cartilage (The tumor may not be exposed to sufficient laser light. Patients with a tumor invading beyond the bronchial wall has a risk of perforation.)
4. Patients with lung cancer who have tracheal stenosis or lesions spreading over a large trachea (Such patients have an increased risk of dyspnoea or asphyxia.)
5. Patients with lung cancer located distal to the subsegmental bronchus (Laser irradiation is generally considered difficult to conduct in such patients.)
6. Patients with esophageal carcinoma invading the aorta (T4) as diagnosed by computed tomography (CT) prior to chemoradiotherapy or radiotherapy (Aorto-oesophageal fistula may occur, possibly resulting in death.)

[Precautions for indications] (Words underlined are additions.)

1. The eligibility of a patient with primary malignant brain tumor or local residual/recurrent oesophageal carcinoma for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the “Clinical studies” section for the histological types of cancers and other information of patients enrolled in the clinical studies, and becoming fully acquainted with the efficacy and safety of the drug product.

2. Radical treatment (e.g., surgical resection, endoscopic treatment [EMR or ESD]) should be prioritized over talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma who are eligible for such radical treatment.
3. The efficacy and safety of talaporfin sodium-mediated PDT have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the following criteria:
 - (a) Lesions classified as T3 or T4, in terms of depth of invasion
 - (b) Lesions with a major axis of >3 cm
 - (c) Lesions in which the circumferential spread is more than half of the luminal circumference
 - (d) Lesions extending to the cervical esophagus

[Precautions for dosage and administration] (Words underlined are additions.)

1. To prepare solution for injection, add 4 mL of Isotonic Sodium Chloride Solution to 1 vial, and stir well until dissolved.
2. The safety and efficacy of the product in combination with intraoperative fluorescence stains or carmustine have not been established in patients with primary malignant brain tumor.
3. In patients with local residual/recurrent oesophageal carcinoma, the irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous injection of the drug product.