This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Report on Investigation Results

November 5, 2021
Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Aminolevulinic acid hydrochloride
[Brand name]	[1] Alabel Oral 1.5 g [2] Alaglio Divided Granules 1.5 g
[Approval holder]	[1] Nobelpharma Co., Ltd. [2] SBI Pharmaceuticals Co., Ltd.
[Indications]	[1] Visualization of malignant tissue during malignant glioma resection [2] Visualization of non-muscle invasive bladder cancer during transurethral resection of the bladder tumor
[Dosage and administration]	[1] The usual adult dosage dissolved in water and orally administered is 20 mg/kg of aminolevulinic acid hydrochloride 3 hours (range: 2-4 hours) before induction of anesthesia during surgery. [2] The usual adult dosage dissolved in water and orally administered is 20 mg/kg of aminolevulinic acid hydrochloride 3 hours (range: 2-4 hours) before cystoscopy insertion.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Aminolevulinic acid hydrochloride (hereinafter referred to as “ALA”) oral preparations (brand name: Alabel Oral 1.5 g, Alaglio Oral 1.5 g) are photodynamic diagnosis (hereinafter referred to as “PDD”) agents, which were approved for marketing on March 25, 2013 for the indication of “visualization of malignant tissue during malignant glioma resection.” The granule formulation of ALA (brand name: Alaglio Divided Granules 1.5 g) is a photodynamic diagnosis agent, which was approved for marketing on September 27, 2017 as indicated for

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

visualization of non-muscle invasive bladder cancer during transurethral resection of the bladder tumor. The approval of Alaglio Oral 1.5 g was withdrawn on April 1, 2019 after Alaglio Divided Granules 1.5 g was approved for marketing as a measure to avoid confusion expected in clinical practice from two products distributed under the same brand name with different indications depending on dosage forms.

ALA is metabolized *in vivo* into protoporphyrin IX (hereinafter referred to as "PPIX"), which is a photo-sensitive substance and accumulates in a tumor-specific manner. In the operative filed, ALA utilizes the nature of PPIX that emits red fluorescent light when excited by blue light and visualizes tumor sites. As a known adverse reaction to ALA, precaution for photosensitivity has been in place in the package inserts of ALA oral agents and granules (hereinafter referred to as the "ALA preparations") since the time of approval for the ALA oral agents. Drugs known to cause photosensitivity and food containing St. John's Wort (hereinafter referred to as "SJW") are noted as contraindications and contraindications for co-administration because of the concern about an enhanced photosensitivity by these drugs and food when the ALA preparations are co-administered with them.

A consultation was requested to the Office of Pharmacovigilance I, Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") by the market authorization holder (hereinafter referred to as "MAH") of ALA granules who intended to remove drugs known to cause photosensitivity and food containing SJW from the contraindications for co-administration on the grounds including that PPIX does not accumulate in a significant amount on the skin following oral administration of ALA and no reported cases of significant and severe photosensitivity that are deemed to be a contraindication for co-administration have been identified and that no overseas package inserts of ALA include a contraindications for co-administration section. PMDA started its discussion on the necessity of revision of the package inserts of ALA preparations in September 2018. Further on June 7, 2021, the Japanese Urological Association and Japan Urological Photodynamic Society submitted a request "Removal of 'patients receiving drugs known to cause photosensitivity: Tetracyclines, sulfonamides, fluoroquinolones, hypericin (St. John's Wort extract), etc., or food containing St. John's Wort' from the CONTRAINDICATIONS for aminolevulinic acid hydrochloride preparations" to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter the "Pharmaceutical Safety Division"). Subsequently on July 1, 2021, another request of a similar intention was submitted by Japan Photodynamic Neurosurgical Society to the Pharmaceutical Safety Division. The reasons for these requests included the following:

- The "drugs known to cause photosensitivity" include drugs that are frequently used after

neurosurgery such as psychotropic drugs (diazepam, carbamazepine, etc.), NSAIDs (ketoprofen, etc.), and hypotensives (nifedipine, etc.) as well as those used in general clinical practice to prevent infections after transurethral surgery such as fluoroquinolones and sulfamethoxazole/trimethoprim (ST) combination drugs.

- The current contraindications limit best options when use of tetracyclines, sulfonamides, fluoroquinolones, or hypericin is absolutely necessary.
- The "drugs known to cause photosensitivity" are extensive with 228 ingredients (as of August 21, 2019) making it extremely difficult to verify the drugs brought in at the time of admission in actual clinical practice.
- The 2 weeks of post-surgery contraindication for co-administration with "drugs known to cause photosensitivity" could profoundly affect the treatment of co-morbidities if no alternative drugs are available. Cases of abandoned photodynamic diagnosis-transurethral resection of the bladder tumor (hereinafter referred to as "PDD-TURBT") have been reported because of a drug contraindicated for co-administration identified among those brought-in at hospital admission.

Of note, the request from Japan Photodynamic Neurosurgical Society also sought, in addition to a revision to reinstate the current contraindications for co-administration as precautions for co-administration, a revision of the period of caution for co-administration to 24 hours before and after administration of ALA on the grounds that 2 weeks of contraindication for co-administration is unlikely to be necessary because the time to maximum plasma concentration and elimination half-life are 0.83 hours following administration and 2.27 hours, respectively, for ALA, and 6.17 hours following administration and 4.91 hours, respectively, for PPIX.

In response to the requests from the above-mentioned academic societies and research foundations, the Pharmaceutical Safety Division requested that PMDA conduct an investigation concerning "Safety related to co-administration with drugs known to cause photosensitivity or ingestion of food containing St. John's Wort in patients receiving aminolevulinic acid hydrochloride preparations."

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Outline of Investigation by PMDA

The “drugs known to cause photosensitivity” which are contraindicated for co-administration with ALA preparations include tetracyclines, sulfonamides, fluoroquinolones, hypericin (St. John's Wort extract), etc., and on these grounds, it was decided that 234 drugs for which precautions regarding photosensitivity are noted in the package insert in Japan under the WARNINGS, CONTRAINDICATIONS, IMPORTANT PRECAUTIONS, Contraindications for Co-administration, Clinically Significant Adverse Reactions, and Other Adverse Reactions sections as of July 31, 2021 would be included in the investigation as “drugs known to cause photosensitivity” (Attachment 1).

1 Current description in Japanese and overseas package inserts of ALA preparations

1.1 Current description in Japanese package inserts

Attachment 2 shows the current description concerning photosensitivity in the Japanese package inserts of ALA preparations.

“Patients should avoid exposure of intense light (such as illuminations of an operation room, direct sunlight, or bright and concentrated indoor light) to the eyes and skin for at least 48 hours following administration of this drug and rest in a room under an illumination below 500 lux” is noted as the risk minimization measure for photosensitivity in the IMPORTANT PRECAUTIONS section. In addition, due to the concern about photosensitivity that is enhanced by co-administration with drugs known to cause photosensitivity and food containing SJW, these drugs are contraindicated and contraindicated for co-administration with a cautionary statement that “administration or ingestion of the drugs or food listed on the left-hand side should be avoided for 2 weeks following administration of this drug” placed under the Contraindications for Co-administration section.

1.2 Current description of overseas package inserts

Attachment 3 shows the current description concerning photosensitivity in the package inserts of ALA preparations (excluding ALA topical agents). It should be noted that indications overseas are solely related to visualization of tumor tissue of malignant glioma. There is not an indication regarding visualization of bladder cancer (as of July 31, 2021).

Current precautions concerning co-administration with “drugs known to cause photosensitivity” and food containing SJW in the package inserts in other countries and regions are as follows:

1.2.1 The UK and EU package inserts (approved in September, 2007)

There is no listing of “drugs known to cause photosensitivity” in the Contraindications section. The Special warnings and precautions for use section states that co-administration with other potentially phototoxic substances (e.g., tetracyclines, sulfonamides, fluoroquinolones, hypericin extract) should be avoided. The Interaction with other medicinal products and other forms of interaction section states that patients should not be exposed to any photosensitizing agent up to 2 weeks after administration of ALA.

1.2.2 The US package insert (approved in June, 2017)

There is no listing of “drugs known to cause photosensitivity” in the CONTRAINDICATIONS section. The WARNINGS AND PRECAUSIONS section states the following: “Do not administer phototoxic drugs (St.John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphoneamides, quinolones and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period.” The DRUG INTERACTIONS section states that patients exposed to a photosensitizing agent may experience a phototoxic skin reaction (severe sunburn) and the following: “Due to the risk of possible phototoxic reactions, avoid administering phototoxic drugs such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines, and topical preparations containing ALA for 24 hours before and after administration of ALA.”

1.2.3 Canadian package insert (approved in September, 2020)

There is no listing of “drugs known to cause photosensitivity” in the CONTRAINDICATIONS section. The WARNINGS AND PRECAUTIONS section states under the heading of “Perioperative considerations” the following: Phototoxic agents (e.g., certain antibiotics [tetracyclines, sulfonamides, fluoroquinolones], hypericin extract) should not be used concurrently for up to 24 hours perioperatively after administration of ALA, unless medically justifiable. Concomitant exposure to any photosensitizing agent with ALA should be avoided. One case of an increased phototoxic reaction (severe sunburn lasting for 5 days) has been reported in a breast cancer patient after co-administration of 40 mg/kg ALA with a hypericin extract. Similarly, the DRUG INTERACTIONS section states the following: ALA is metabolized in the body into PPIX, which in the skin can lead to phototoxic reactions. Patients exposed to a photosensitizing agent may experience a phototoxic skin reaction (severe sunburn). Avoid administering phototoxic drugs (e.g. certain antibiotics [tetracyclines, sulfonamides, fluoroquinolones griseofulvin] thiazide diuretics, sulfonylureas, phenothiazines, topical preparations containing ALA HCl, and hypericin extract) for 24 hours before and after administration of ALA. SJW is considered phototoxic and should be

avoided for 24 hours before and after administration of ALA.

1.2.4 Package inserts in other countries

The description in the package inserts of ALA with indications of visualization of tumor tissues in malignant glioma in Australia (approved in November 2013) and New Zealand (approved in September 2015) were similar to that of the UK and EU package inserts.

2 Status of photosensitivity onset and co-administration with "drugs known to cause photosensitivity" or food containing SJW in association with ALA preparations

2.1 In clinical studies up to application for marketing authorization

Attachment 4 shows the light interception time, listing of drugs contraindicated for co-administration, and incidence of cases involving photosensitivity[1] in Japanese and overseas clinical studies of ALA oral agents and granules.

In the Japanese clinical study with ALA oral agents (1 study, 45 cases included in the safety analysis) "drugs known to cause photosensitivity" were co-administered in 36 cases. No cases of photosensitivity were identified in the 45 cases subjected to the safety analysis. In the overseas clinical studies (6 studies, 562 cases in total included in the safety analysis), co-administration with "drugs known to cause photosensitivity" was ruled out in 21 cases, and the co-administration status was unknown in 541 cases. The status of co-ingestion of food containing SJW was unknown in all the cases. Of the 562 cases included in the safety analysis, 3 events related to photosensitivity were identified in 2 cases, the severity being mild in both cases.

In the Japanese clinical study with ALA granules (2 studies, 123 cases in total included in the safety analysis) "drugs known to cause photosensitivity" were co-administered in 75 cases. No cases involving photosensitivity were identified among the 123 cases included in the safety analysis.

No cases of co-administration with food containing SJW had been identified in the clinical studies conducted up to the application for marketing authorization.

2.2 Post-marketing situation

2.2.1 Estimated number of patients treated

The post-marketing cumulative number of patients treated with ALA preparations in Japan

[1]Conditions to retrieve cases involving photosensitivity: [HLT] 10072982/Photosensitivity and photodermatosis conditions and cases of photosensitivity suspected based on clinical course, etc.

is 26 294 for Alabel Oral, 98 for Alaglio Oral[2], and 15 107 for Alaglio Divided Granules as estimated by respective MAHs (as of July 31, 2021).

The post-marketing cumulative number of patients treated with ALA (used for visualization of malignant glioma) worldwide is 128 943 as estimated by the MAH of ALA granules (as of July 31, 2021).

2.2.2 Spontaneous reports

The number of cases involving photosensitivity collected in the spontaneous adverse reaction reporting[1] is shown in Attachment 5.

Photosensitivity has been reported as an adverse reaction in Japan in 6 cases with ALA oral agents[3] (1 serious, 5 non-serious cases) and in 20 cases with ALA granules (1 serious, 19 non-serious cases). Co-administration with “drugs known to cause photosensitivity” or food containing SJW was ruled out in all of the 6 cases treated with ALA oral agents. The co-administration was identified in 4 cases (1 serious, 3 non-serious cases), ruled out in 4 cases (4 non-serious cases) and unknown in 12 cases (12 non-serious cases) of the 20 cases treated with ALA granules.

Photosensitivity has been reported as an adverse reaction overseas in 17 cases (1 serious, 13 non-serious, 3 with unknown seriousness) treated with ALA (used for visualization of malignant glioma). Co-administration with “drugs known to cause photosensitivity” or food containing SJW was identified in 3 cases (all non-serious) and unknown in 14 cases (1 serious, 10 non-serious, 3 with unknown seriousness).

2.2.3 Use-results survey (post-marketing surveillance)

A use-results survey has been conducted for Alabel Oral, Alaglio Oral[2], and Alaglio Divided Granules in an all-case manner. (Attachment 6)

Of the 648 cases registered in the use-results survey for Alabel Oral, the “drugs known to cause photosensitivity” were co-administered in 91 cases. No events related to photosensitivity developed in the 91 co-administration cases. A photosensitivity-related event was observed in 1 (non-serious) of the 557 cases in which the co-administration was not confirmed.

In 43 of the 98 cases registered in the use-results survey for Alaglio Oral, “drugs known to cause photosensitivity” were co-administered. No events related to photosensitivity were identified among the 98 cases.

In 368 of the 794 cases registered in the use-results survey for Alaglio Granules, the “drugs

[2] Approval was withdrawn for Alaglio Oral in April 2019.
[3] All reported with Alabel Oral

known to cause photosensitivity" were co-administered. Events related to photosensitivity were observed in 3 of the 368 co-administration cases. The 3 cases were all non-serious. Events related to photosensitivity were observed in 5 (all non-serious) of the 426 cases in which co-administration was not confirmed.

There were no cases in which co-administration with food containing SJW was identified in the use-results survey.

2.2.4 Research papers and reported measures

No studies on photosensitivity were included in those notified to PMDA by the MAH of ALA oral agents or ALA granules by July 31, 2021. Two of the reports on foreign measures received by PMDA concerned photosensitivity, and neither concerned co-administration with the "drugs known to cause photosensitivity" or food containing SJW.

3 Published literature, etc. on photosensitivity occurring following administration of ALA

3.1 Published literature, etc.

Using PubMed, Google Search, and CiNii Articles (see Attachment 7 for search conditions), published literature on photosensitivity associated with ALA was searched and literature and other materials that described co-administration with other drugs were retrieved. The retrieved literature and other materials were investigated excluding non-oral administration routes (such as intravesical injection or percutaneous administration). As a result, the following 2 overseas studies and statements in PDR.net, which is widely used by clinicians in the US as a source of drug information were identified.

(1) The 2 studies both reported an identical case who developed photosensitivity following administration of ALA and used SJW extract simultaneously.

In a study conducted overseas, ALA 40 mg/kg (2-fold the approved dosage in Japan) was administered to patients with breast cancer for photodynamic diagnosis. Serious photosensitivity developed in 1 of the 16 patients, and it was found that the patient had taken SJW extract prior to ALA administration[4]. The case was a women aged 47 years. Burning erythematous rash was noted 6 hours after administration of ALA and severe swelling developed in the face, neck, and the upper limbs, or only in light-exposed body parts. With an oral corticosteroid administered for 3 days, photosensitivity completely remitted within 10 days. In addition, to investigate an interaction between the 2 agents, ALA and SJW extract were added simultaneously to a culture media of keratinocytes,

[4] Lander DP et al., Br J Cancer 2001; 84, 33-7.

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

and the media was illuminated. Synergistic inhibition of colony formation was observed as a result[5].

(2) PDR.net[6] states in the DRUG INTERACTIONS section for ALA that “St. John's wort has been reported to increase the phototoxicity associated with photosensitizing agents used in photodynamic therapy and that, although interactions have not been reported, phototoxicity is possible in theory.” The section also states for other products that “co-administered drugs may cause photosensitivity” and that “prevention of photosensitivity includes adequate protection from sources of UV radiation and the use of protective clothing and sunscreens on exposed skin.” Of note, the page also states photosensitivity associated with ALA is classified into a “Mild” adverse reaction in the PDR.net.

In addition, a search using MEDLINE and JAPIC-Q (see Attachment 8 for search conditions) identified 5 overseas articles. All of them were case reports, concerning a total of 6 cases of photosensitivity. 1 case had identical information as is described in the second report in (1), 4 were of an ALA topical agent(s), and the details were unknown for the remaining 1 case.

3.2 Current description in Japanese and overseas standard textbooks, clinical practice guidelines, and other related materials

Japanese and western standard textbooks, clinical practice guidelines, and other related materials related to malignant glioma[7] (see Attachment 9 for search conditions) were

[5] Lander DP et al., Br J Dermatol 2001; 144: 916-8.
[6] PDR.net, Amino levulinic acid Drug summary (confirmed on October 12, 2021) https://www.pdr.net/drug-summary/Ameluz-aminolevulinic-acid-hydrochloride-23964
[7] The following clinical practice guidelines were examined:

- The Laser Therapy Safety Guidelines for Neurosurgical Diseases, Journal of Japan Society for Laser Surgery and Medicine, Volume 32, supplement (2011)
- The Clinical Practice Guidelines for Brain Tumor 2019 by The Japan Society for Neuro-Oncology
- The Safety Guidelines for Photodynamic Therapy in Patients with Locally Residual Recurrent Oesophageal Carcinoma after Chemoradio or Radiotherapy by the Japan Photodynamic Association (2015)
- Neurosurgery II Revised edition 12, Tomio Ota (editor) (2016) Kinpodo
- Fluorescence-Guided Neurosurgery; Neuro-oncology and Cerebrovascular Applications edited by Constantinos G. Hadjipanayis and Walter Stummer (2019), Thiem Medical Publishers, Inc.
- NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY Central Nervous System Cancers, Version 3.2020, J Natl Compr Canc Netw 2020; 18:1537–70.
- Brain tumours (primary) and brain metastases in adults, NICE guideline Published:11 July 2018
- European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas, Lancet Oncology, 2017; 18:e315-e329.
- Clinical Practice Guidelines: High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 2014; 25 (Supplement 3): iii93–iii101.
- Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions」Neuro-Oncology 2020; 22: 1073-113. 1073–113.
- “Intracranial gliomas Part I Surgery” MF Chernov, Y Muragaki, S Kesari and IE McCutcheon (Eds)

searched for language concerning photosensitivity associated with ALA. The guidelines containing related descriptions and the specific language are as follows:

- The Laser Therapy Safety Guidelines for Neurosurgical Diseases (2011[8])
  Patients with a history of photosensitivity or porphyria and patients with hypersensitivity to ALA or Laserphyrin are listed as contraindications for PDD in the neurosurgical field. No description related to co-administration was found either with “drugs known to cause photosensitivity” or with food containing SJW.
- Fluorescence-Guided Neurosurgery–Neuro-oncology and Cerebrovascular Applications (2019)
  ALA enhances photosusceptibility of the skin as an adverse reaction to the drug. When ALA is used, avoidance of intense light, especially direct sun exposure is recommended over a period of 24 hours after administration. It is stated that skin erythema has been rarely observed and no serious burns have been reported. No description related to co-administration was found either with “drugs known to cause photosensitivity” or with food containing SJW.

The Japanese clinical practice guidelines concerning bladder cancer (Clinical Practice Guidelines for Bladder Cancer 2019, The Japanese Urological Association) were also reviewed for descriptions regarding photosensitivity associated with ALA but none were found. (See Attachment 9 for search conditions.)

IV. PMDA’s judgement based on the investigation results

1. Removal of “drugs known to cause photosensitivity” and “food containing SJW” from the CONTRAINDICATIONS section and Contraindications for Co-administration section to be listed under the Precautions for Co-administration section

Given the investigation so far described, PMDA considers, for the reasons as follows, that the co-administration of ALA with “drugs known to cause photosensitivity” and food containing SJW may be removed from the contraindications for co-administration provided that the risk minimization measures such as avoiding intense light exposure of the patients are properly taken.

- The “drugs known to cause photosensitivity” include drugs that are frequently used after neurosurgery such as psychotropic drugs (diazepam, carbamazepine, etc.), NSAIDs

(2018). Intracranial gliomas Part I Surgery. Karger

[8]ALA was approved in Japan in 2013.

(ketoprofen, etc.), and hypotensives (nifedipine, etc.), as well as those used in general clinical practice for prevention of infections after transurethral surgery such as fluoroquinolones and ST combination preparations. Contraindicating these drugs for co-administration imposes restrictions on the use of ALA, thereby hampering actual clinical practice.

- ALA is used in surgery to visualize tumors and, therefore, patients are basically managed under hospitalization where they are not likely to be exposed to intense light, allowing prevention of photosensitivity. Besides, the current IMPORTANT PRECAUTIONS section includes a cautionary statement that patients should avoid intense light at least for 48 hours following administration of ALA.
- Although photosensitivity may be enhanced by the co-administration, no data have been identified in the adverse reactions reports, published literature, textbooks, clinical practice guidelines, or other related materials in Japan and overseas that raise a particular concern in clinical practice regarding the co-administration with “drugs known to cause photosensitivity” as well as with food containing SJW.
- Neither “drugs known to cause photosensitivity” nor food containing SJW are contraindicated for co-administration in the package inserts of ALA preparations in certain overseas countries and regions.
  - Hypericin, which is an SJW extract, may be removed as an example of “drugs known to cause photosensitivity” because hypericin is not approved as a drug in Japan.

2. Period of caution for co-administration with “drugs known to cause photosensitivity” and food containing SJW

The current Japanese package inserts of ALA preparations specify 2 weeks after administration of ALA as the period to avoid co-administration with “drugs known to cause photosensitivity” or foods containing SJW, and the respective MAHs of ALA oral agents and ALA granules cite for the reason the UK package insert that they found to note 2 weeks for the period.

Regarding the period of precautions for co-administration in the current discussion of revision of the package insert, Japan Photodynamic Neurosurgical Society has requested 24 hours before and after administration, the duration US package inserts specify, based on the maximum plasma concentrations and half elimination lives of ALA and PPIX.

Besides, the MAH of ALA granules explains that 24 hours after administration is appropriate for the duration of precautions for co-administration as Japan Photodynamic

Neurosurgical Society requested and that precautions for co-administration for 24 hours before administration of ALA are not necessary for the reasons as follows:

- The ALA granules in Japan share the same dosage and administration with the ALA preparations overseas, although with different indications.
- A clinical pharmacology study performed in Europe where ALA 20 mg/kg was orally administered has reported that PPIX plasma levels were almost not detectable in 24 hours after administration and the reduced minimal erythema dose as an indication of enhanced photosusceptibility returned to normal in 48 hours after administration.[9]
- In the US where ALA preparations were approved with 24 hours before and after administration as the period to avoid co-administration with drugs that exhibit phototoxicity and 48 hours after administration to avoid intense light, only 1 (non-serious) case involving photosensitivity has been reported by July 2020.
- Taking account that “48 hours after administration” is specified as a period to avoid intense light in the Japanese package inserts as in the US, patient management with “24 hours after administration of this drug” as the period of caution for co-administration in line with the US, instead of 2 weeks after ALA administration, would not impair patient safety. Neither Japanese nor European package inserts specify any precautions for the 24 hours before administration of this drug. No major effects by the absence of such precautions have been observed on the incidence of photosensitivity so far.

PMDA considers the period of caution for co-administration with “drugs known to cause photosensitivity” or food containing SJW as follows while seeking that a careful decision be made taking into account the Expert Discussion.

- By avoiding intense light exposure for at least 48 hours after administration of ALA, the risks associated with phototoxicity will be minimized even if enhanced by concomitant use of these drugs or food before or after administration of ALA, and no information has been identified in the Japanese or overseas adverse drug reaction reports, published literature, textbooks, or clinical practice guidelines that raises particular clinical safety concerns regarding co-administration with “drugs known to cause photosensitivity” or foods containing SJW. Therefore, PMDA believes that 2 weeks after administration of ALA are not highly required as the period of caution for the co-administration.
- Regarding the appropriateness of switching from the current “2 weeks after administration” for contraindication for co-administration to “24 hours after

[9] Alabel Oral, Alaglio Oral Summaries of product application 2.5.3.2 Comparison of Plasma pharmacokinetics, 2.5.3.3 Pharmacodynamic evaluation

administration" for precautions for co-administration, considering the specified period of at least 48 hours to avoid intense light against the risk of photosensitivity associated with ALA, precaution is also necessary for co-administration with "drugs known to cause photosensitivity" or food containing SJW for the same period with a statement that "drugs known to cause photosensitivity" and food containing SJW should preferably be avoided whenever possible for 48 hours after administration of ALA.

3. Proposed revision

The revision of precautions proposed by PMDA based on the discussion described in section 1 and 2 above is presented in Attachment 10.1. The revisions proposed by the MAH of ALA granules and the MAH of ALA oral agents are presented in Attachment 10.2 and Attachment 10.3, respectively. (Attachment 10 is not included here. See the Detailed information on revisions of PRECAUTIONS for Attachment 10.1.)

V. Expert Discussion

1. Removal of "drugs known to cause photosensitivity" and "food containing SJW" from the CONTRAINDICATIONS section and Contraindications for Co-administration section to be listed for Precautions for Co-administration

The PMDA's decision that the co-administration of ALA with "drugs known to cause photosensitivity" and food containing SJW may be removed from the contraindications for co-administration on the premise that risk minimization measures such as avoidance of intense light exposure are appropriately implemented was supported by the expert advisors.

An expert advisor commented on the importance of information provision and pharmacovigilance after the revision as well as the necessity of reconsidering this revision if data should be accumulated indicating high risks associated with the co-administration. Also given the comment, PMDA instructed the MAHs to explore specific plans of information provision as well as pharmacovigilance after the revision, and the MAHs responded that detailed investigations will be performed for cases developing photosensitivity and safety measures will be explored as necessary without delay.

2. Period of caution for co-administration with "drugs known to cause photosensitivity" and food containing SJW

PMDA's opinion that "drugs known to cause photosensitivity" and food containing SJW should preferably be avoided whenever possible for 48 hours after ALA administration (48 hours following initiation of ALA administration) was supported by expert advisors.

The PMDA's decision that the period of caution for use of the drugs or food prior to ALA administration is not necessary at present was generally supported. An opinion as follows was expressed from an expert advisor as well.

- Administration of the drugs known to cause photosensitivity before ALA administration may also enhance the photosensitivity due to ALA with the effects of such drugs. Co-administration of such drugs should preferably be avoided prior to ALA administration. For the period of caution for co-administration, 24 hours before ALA administration as in the US should be appropriate. For the period of caution for co-administration after ALA administration, on the other hand, 48 hours should be acceptable, which would allow co-administration when necessary.

In response to the opinion, PMDA considered the addition of a period of caution for co-administration prior to ALA administration. At present, no data have been obtained that support the necessity of adding a period of caution for co-administration prior to ALA administration. Moreover, even if phototoxicity is enhanced following ALA administration, the risk is to be minimized through having patients avoid intense light exposure for at least 48 hours following ALA administration. PMDA believes the addition of 24 hours prior to ALA administration is not necessary. Taking into account, on the other hand, the theoretical possibility of photosensitivity enhanced by such drugs or food if "drugs known to cause photosensitivity" or food containing SJW are administered 24 hours prior to ALA administration, PMDA decided that it would be critical after the revision to collect information regarding the onset of photosensitivity (including information on the relevant co-administration) and assess such information in order to consider the necessity of additional safety measures, and instructed the MAHs to explore specific contents of the post-revision pharmacovigilance plans. The MAHs responded as described in V.1.

VI. Overall Evaluation

PMDA concluded that precautions in the package insert may be revised according to Attachment 10.1. (Attachment 10.1 is not included here. See the Detailed information on Revisions of PRECAUTIONS.)

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Attachment 1. "Drugs known to cause photosensitivity" 234 drugs lists* (As of July 31, 2021)

Therapeutic Category No.	Therapeutic Category	Number of drugs	Non-proprietary name
112	Hypnotics and sedatives, antianxietics	2 drugs	Alprazolam, chlordiazepoxide
113	Antiepileptics	2 drugs	Ethosuximide, carbamazepine
114	Antipyretics, analgesics and anti-inflammatory agents	12 drugs	Ampiroxicam, etodolac, zaltoprofen, diclofenac sodium, dimetotiazine mesilate, sulindac, celecoxib, tiaprofenic acid, nabumetone, naproxen, piroxicam, meloxicam
116	Antiparkinsonian agents	4 drugs	Amantadine hydrochloride, safinamide mesilate, promethazine, promethazine methylenedisalicylate
117	Psychotropic agents	30 drugs	Amantadine hydrochloride, aripiprazole, aripiprazole hydrate, imipramine hydrochloride, olanzapine, carbamazepine, chlorpromazine hydrochloride, chlorpromazine phenolphthalinate, chlorpromazine hydrochloride, sertraline hydrochloride, duloxetine hydrochloride, paroxetine hydrochloride hydrate, haloperidol, haloperidol decanoate, pipamperone hydrochloride, fluphenazine decanoate, fluphenazine maleate, fluvoxamine maleate, prochlorperazine maleate, prochlorperazine mesilate, propericiazine, perphenazine, perphenazine fendizoate, perphenazine maleate, venlafaxine hydrochloride, maprotiline hydrochloride, levomepromazine maleate, levomepromazine hydrochloride, perphenazine hydrochloride, blonanserin
122	Skeletal muscle relaxants	1 drug	Dantrolene sodium hydrate
124	Antispasmodics	1 drug	Afloqualone
131	Agents for ophthalmic use	1 drug	Verteporfin
133	Antimotionsickness agents	1 drug	Dimenhydrinate
212	Antiarrhythmic agents	3 drugs	Amiodarone hydrochloride, quinidine sulfate hydrate, metoprolol tartrate
213	Diuretics	8 drugs	Acetazolamide, acetazolamide sodium, triamterene, trichlormethiazide,

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Therapeutic Category No.	Therapeutic Category	Number of drugs	Non-proprietary name
			hydrochlorothiazide, furosemide, benzylhydrochlorothiazide, mefruside
214	Antihypertensives	34 drugs	Azilsartan/amlodipine besilate, azelnidipine, imidapril hydrochloride, irbesartan/amlodipine besilate, irbesartan/trichlormethiazide, indapamide, enalapril maleate, olmesartan medoxomil/azelnidipine, captopril, candesartan cilexetil, candesartan cilexetil/amlodipine besilate, candesartan cilexetil/hydrochlorothiazide, cilnidipine, telmisartan/amlodipine besilate/hydrochlorothiazide, doxazosin mesilate, tripamide, nicardipine hydrochloride, nilvadipine, valsartan, valsartan/amlodipine besilate, valsartan/cilnidipine, valsartan/hydrochlorothiazide, barnidipine hydrochloride, hydrochlorothiazide, felodipine, benazepril hydrochloride, benzylhydrochlorothiazide/reserpine, manidipine hydrochloride, metoprolol tartrate, lisinopril, losartan potassium, losartan potassium/hydrochlorothiazide
217	Vasodilators	8 drugs	Amlodipine besilate, enalapril maleate, candesartan cilexetil, diltiazem hydrochloride, nitrendipine, nifedipine, benidipine hydrochloride, lisinopril
218	Agents for hyperlipidemias	7 drugs	Atorvastatin calcium, ezetimibe/atorvastatin calcium hydrate, simvastatin, fenofibrate, pravastatin sodium, fluvastatin sodium, bezafibrate
219	Other cardiovascular agents	3 drugs	Amlodipine besilate/atorvastatin calcium hydrate, selexipag, limaprost alfadex
229	Other agents affecting respiratory organs	1 drug	Omalizumab (genetical recombination)
232	Agents for peptic ulcer	3 drugs	Esomeprazole magnesium hydrate, omeprazole, omeprazole sodium hydrate
239	Other agents affecting digestive organs	4 drugs	Aprepitant, infliximab (genetical recombination), olanzapine, fosaprepitant meglumine
245	Adrenal hormone preparations	1 drug	Betamethasone/d-chlorpheniramine maleate
249	Other hormone preparations (including	1 drug	Danazol

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Therapeutic Category No.	Therapeutic Category	Number of drugs	Non-proprietary name
	antihormone preparations)		
259	Other agents for uro-genital and anal organ	1 drug	Vardenafil hydrochloride hydrate
263	Dermatics for purulence	2 drugs	Sulfadiazine, sulfadiazine silver
264	Analgesics, anti-itchings, astrigents and anti-inflammatory agents	4 drugs	Ketoprofen, suprofen, dexamethasone/glyteer, dry distillation tar of defatting soybean
269	Other agents for epidermis	2 drugs	Clindamycin/benzoyl peroxide, methoxsalen
313	Vitamin B preparations (excluding Vitamin B1)	1 drug	Pyridoxine hydrochloride
322	Mineral preparations	1 drug	Soluble ferric pyrophosphate
339	Other agents relating to blood and body fluids	3 drugs	Clopidogrel sulfate, clopidogrel sulfate/aspirin, cilostazol
392	Antidotes	2 drugs	Calcium folinate, levofolinate calcium hydrate
394	Agents for treatment of gout	1 drug	Benzbromarone
396	Antidiabetic agents	9 drugs	Acetohexamide, gliclazide, glyclopyramide, glibenclamide, glimepiride, chlorpropamide, pioglitazone hydrochloride/glimepiride, voglibose, mitiglinide calcium hydrate/voglibose
399	Agents affecting metabolism, n.e.c. (not elsewhere classified)	7 drugs	Adalimumab (genetical recombination), iguratimod, etanercept (genetical recombination), certolizumab pegol (genetical recombination), hydroxychloroquine sulfate, pirfenidone, methotrexate
421	Alkylating agents	2 drugs	Dacarbazine, temozolomide
422	Antimetabolic agents	6 drugs	Capecitabine, tegafur, tegafur/uracil, tegafur/gimeracil/oteracil potassium, doxifluridine, fluorouracil
424	Antineoplastic preparations	2 drugs	Irinotecan hydrochloride hydrate, paclitaxel

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Therapeutic Category No.	Therapeutic Category	Number of drugs	Non-proprietary name
	extracted from plants		
429	Other antitumor agents	30 drugs	Alectinib hydrochloride, imatinib mesilate, entrectinib, eribulin mesilate, erlotinib hydrochloride, encorafenib, osimertinib mesilate, crizotinib, cetuximab sarotalocan sodium (genetical recombination), dasatinib, tazemetostat hydrobromide, dabrafenib mesilate, talaporfin sodium, tirabrutinib hydrochloride, tucidinostat, trametinib dimethyl sulfoxide, niraparib tosilate hydrate, nilotinib hydrochloride hydrate, vandetanib, bicalutamide, binimetinib, brigatinib, flutamide, bexarotene, pembrolizumab (genetical recombination), vemurafenib, bosutinib hydrate, bosutinib hydrochloride, ponatinib hydrochloride, porfimer sodium, sirolimus
441	Antihistamines	6 drugs	d-Chlorpheniramine maleate, promethazine hibenzate, promethazine, promethazine hydrochloride, promethazine methylenedisalicylate, mequitazine
442	Agents for stimulation therapy	2 drugs	Auranofin, bucillamine
449	Other antiallergic agents	1 drug	Omalizumab (genetical recombination)
614	Antibiotic preparations acting mainly on gram-positive bacteria and mycoplasma	2 drugs	Azithromycin hydrate, clarithromycin
615	Antibiotic preparations acting mainly on gram-positive, gram-negative bacteria, and rickettsia and chlamydia	2 drugs	Doxycycline hydrochloride, minocycline hydrochloride
617	Antibiotic preparations acting mainly on mold	1 drug	Voriconazole
621	Sulfonamide preparations	1 drug	Salazosulfapyridine

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Therapeutic Category No.	Therapeutic Category	Number of drugs	Non-proprietary name
623	Antileprotic agents	1 drug	Clofazimine
624	Synthetic antibacterials	11 drugs	Ofloxacin, sitafloxacin hydrate, ciprofloxacin, ciprofloxacin hydrochloride, tosufloxacin tosilate hydrate, norfloxacin, prulifloxacin, garenoxacin mesilate hydrate, levofloxacin hydrate, lomefloxacin, hydrochloride
625	Anti-virus agents	9 drugs	Aciclovir, atazanavir sulfate, amantadine hydrochloride, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, nevirapine, valaciclovir hydrochloride, valaciclovir hydrochloride, ribavirin
629	Other chemotherapeutics	5 drugs	Itraconazole, sulfamethoxazole/trimethoprim, terbinafine hydrochloride, flucytosine, imiquimod
639	Other biological preparations	3 drugs	Interferon alfa (NAMALWA), peginterferon alfa-2a (genetical recombination), peginterferon alfa-2b (genetical recombination)
729	Other diagnostic agents (excluding extracorporeal diagnostic medicines)	2 drugs	Aminolevulinic acid hydrochloride, fluorescein

* The 11 active ingredients (amantadine hydrochloride, enalapril maleate, omalizumab (genetical recombination), olanzapine, carbamazepine, candesartan cilexetil, hydrochlorothiazide, promethazine methylenedisalicylate, metoprolol tartrate, and lisinopril) which are categorized to multiple therapeutic groups are counted as 1 drug.

* List of drugs submitted by MAHs explained to medical institutions as drugs known to cause photosensitivity.

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Attachment 2. Current description of Japanese package inserts

Contraindications
Patients receiving drugs known to cause photosensitivity: Tetracyclines, sulfonamides, fluoroquinolones, hypericin (St. John's Wort extract), etc., or food containing St. John's Wort

2. Important Precautions
"Patients should avoid exposure of intense lights (such as illuminations of an operation room, direct sunlight, or bright and concentrated indoor lights) to the eye and skin for at least 48 hours following administration of this drug and rest in a room under an illumination below 500 lux" Note 1
Note 1: The illumination criteria of the Japanese Industrial Standard (JIS Z 9110) define the hospital illuminance as 100 to 200 lux for patients rooms, 200 to 500lux for general laboratories and dining rooms, and 300 to 750 lux for examination rooms and pharmacies.

3. Drug Interactions
(1) Contraindications for Co-administration (This drug should not be co-administered with the following drugs or food.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs known to cause photosensitivity: Tetracyclines, sulfonamides, fluoroquinolones, hypericin (St. John's Wort extract), etc.	Photosensitivity may occur. Administration of the drugs or ingestion of the food listed on the left-hand should be avoided for 2 weeks after administration of this drug.	This drug is metabolized *in vivo* into a photo-sensitive substance. Co-administration of the drugs or ingestion of the food listed on the left-hand may enhance photosensitivity.
Food containing St. John's Wort		

4. Adverse Reactions
(2) Other Adverse Reactions
Photosensitivity, photodermatosis
(N/A)

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Attachment 3. Descriptions in overseas package inserts

	Date of approval	Descriptions
UK, EU package insert	September, 2007	4.3 No related descriptions in the Contraindications section 4.4 Special warnings and precautions for use After administration of this medicinal product, exposure of eyes and skin to strong light sources (e.g. operation illumination, direct sunlight or brightly focused indoor light) should be avoided for 24 hours. Co-administration with other potentially phototoxic substances (e.g. tetracyclines, sulfonamides, fluoroquinolones, hypericin extracts) should be avoided (see also section 5.3). 4.5 Interaction with other medicinal products and other forms of interaction Patients should not be exposed to any photosensitising agent up to 2 weeks after administration of Gliolan. 4.8 Undesirable effects Photosensitivity reaction, photodermatosis
US package insert	June, 2017	4 No related descriptions in the CONTRAINDICATIONS section 5 WARNINGS AND PRECAUTIONS 5.1 Risk of Phototoxic Reaction Due to the risk of phototoxic reactions, do not administer phototoxic drugs (St.John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphoneamides, quinolones and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period [see Drug Interactions (7)]. Reduce exposure to sunlight or room lights for 48 hours after administration of Gleolan. 7 DRUG INTERACTIONS Phototoxic Drugs Patients exposed to a photosensitizing agent may experience a phototoxic skin reaction (severe sunburn). Due

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	Date of approval	Descriptions
		to the risk of possible phototoxic reactions, avoid administering phototoxic drugs such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines, and topical preparations containing ALA for 24 hours before and after administration of Gleolan
Canadian package insert	Septmeber, 2020	2 No related descriptions in the CONTRAINDICATIONS section 6 WARNINGS AND PRECAUTIONS Peri-Operative Considerations Aminolevulinic Acid induces a photosensitizing agent (PpIX). Patients are to avoid direct sunlight and postoperatively reduce exposure to room lights for 48 h after administration of Gleolan to avoid any skin sensitization. In addition, due to the risk of possible phototoxic reactions, phototoxic agents (e.g., certain antibiotics [tetracyclines, sulfonamides, fluoroquinolones], hypericin extract) should not be used concurrently for up to 24 hours perioperatively after administration of Gleolan, unless medically justifiable (see DRUG INTERACTIONS). Concomitant exposure to any photosensitizing agent and Aminolevulinic Acid HCl should be avoided. One case of an increased phototoxic reaction (severe sunburn lasting for 5 days) has been reported in a breast cancer patient after coadministration of 40 mg/kg Aminolevulinic Acid HCl with a hypericin extract. 8 DRUG INTERACTIONS 8.1 Overview Aminolevulinic Acid is metabolized in the body into PpIX, which in the skin can lead to phototoxic reactions. Therefore, caution is advised for the administration of therapeutic agents that may also induce phototoxic reactions. 8.2 Drug-Drug Interactions Patients exposed to a photosensitizing agent may experience a phototoxic skin reaction (severe sunburn). Due to the risk of possible phototoxic reactions, avoid administering phototoxic drugs (e.g. certain antibiotics [tetracyclines, sulfonamides, fluoroquinolones griseofulvin] thiazide diuretics, sulfonylureas, phenothiazines,

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	Date of approval	Descriptions
		topical preparations containing ALA HCl, and hypericin extract) for 24 hours before and after administration of Gleolan. In vitro studies suggest that phenytoin and other anti-convulsants may decrease cellular PpIX accumulation following Gleolan dosing. 8.3 Drug-Herb Interactions St. John's wort is considered phototoxic and should be avoided for 24 hours before and after administration of Gleolan.
Australian package insert	November, 2013	Similar descriptions as in the UK, EU package inserts
New Zealand's package insert	Septmeber, 2015	Similar descriptions as in the UK, EU package inserts

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Attachment 4. Summary of clinical studies and occurrence of photosensitivity

(1) Shading periods and contraindications for co-administration for ALA oral agents specified in clinical studies in Japan and overseas are as shown in Table 1.

Table 1. Summary of clinical studies in Japan and overseas for ALA oral agents

	Study numbers, development phases, and shading periods	Specified contraindications for co-administration
Japanese clinical study 1 study	NPC-07-1 Phase III study 24 hours after administration	Co-administration of tetracylines, sulufonamides (excluding temozolomide), quinolones, sulfonylureas, and hypericine (including dietary supplements) were contraindicated during the clinical study.
Foreign clinical studies 6 studies	MC-ALS.20/BV Phase I study 24 hours after administration	Concomitant drugs or combination therapies are prohibited during the clinical study.
	MC-ALS.8-I/GLI Phase I/II study 24 hours after administration	There was no limitation for concomitant drugs or food. Administration of drugs with phototoxicity was discontiniued for 24 hours after administration of ALA when meidically justifiable.
	MC-ALS.28/GLI Phase II study 48 hours after administration	
	MC-ALS.30/GLI Phase II study 24 hours after administration	
	MC-ALS.3/GLI Phase III study 24 hours after administration	
	MC-ALS.32/GLI Phase III study 24 hours after administration	

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Occurrence of photosensitivity-related events in foreign clinical studies is shown in Table 2. No cases of photosensitivity-related events were reported in the Japanese clinical study.

Table 2. Occurrence of photosensitivity-related events for ALA oral agents in foreign clinical studies

No	Year of onset	Country	Adverse reactions (PT)	Severity	Outcome	Shading period	Time from administration to onset	Co-administration with drugs known to cause photosensitivity.
1	2000	Germany	Photodermatosis	Mild	Recovered	Unknown	Day of administration	Unknown
	2000	Germany	Photosensitivity reaction	Mild	Recovered	Unknown	2 days	Unknown
2	2003	Germany	Photosensitivity reaction	Mild	Unknown	Unknown	48h	Unknown

(2) Shading periods and contraindications for co-administration specified in Japanese clinical studies (2 studies) for ALA granules are shown in Table 3.

Table 3. Summary of Japanese clinical studies for ALA granules

Study numbers and development phases	Shading period	Specified contraindications for co-administration
Phase II/III study in Japan (ALA-BC-1)	24 hours after administration	Concomitant use of drugs shown below was prohibited for 14 days after the consent was obtained. 1) Antibacterials: tetracyclines, sulufonamides Hypoglycemic drugs: sulfonylureas Others: Hypericine extract (including dietary supplements) 2) Intravesical infusion therapy of BCG, anti-cancer drugs, etc., drugs for photodynamic therapy, etc. 3) Investigational drugs other than this drug

Japanese Phase III study（SPP2C101）	48 hours after administration	Concomitant use of drugs shown below was prohibited for 14 days after administration. 1) Drugs known to cause photosensitivity: tetracyclines, fluoroquinolones, sulfonamides, hypericine (St. Johan's wort extract), etc., food containing St. John's wort 2) Drugs for photodynamic therapy, etc. 3) Intravesical infusion therapy of BCG, anti-cancer drugs, etc. 4) Investigational drugs other than this drug

No cases of photosensitivity-related events were reported.

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Attachment 5. Occurrence of photosensitivity in spontaneous reports

(1) Occurrence of photosensitivity-related events for ALA oral agents in spontaneous reports in Japan is shown in Table 4.

Table 4. Occurrence of photosensitivity-related events for ALA oral agents in spontaneous adverse drug reactions reports in Japan*1

No	Year of onset	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with "drugs known to cause photosensitivity" or food containing SJW.
1	2014	Photosensitivity reaction	Serious*2	Recovered	60 hours	3 days	None
2	2014	Photosensitivity reaction	Non-serious	Recovered	2 days	Approximately 2 weeks	None
3	2015	Photosensitivity reaction	Non-serious	Recovered	2 days	Approximately 2 weeks	None
4	2015	Photosensitivity reaction	Non-serious	Recovered	2 days	Approximately 2 weeks	None
5	2017	Photosensitivity reaction	Non-serious	Recovered	Unknown	0 day	None
6	2018	Photosensitivity reaction	Non-serious	Recovered	Unknown	0 day	None

*1 Alabel Oral was administered in all the cases.
*2 The serious case was recovered using only steroids.

(2) Occurrence of photosensitivity-related events for ALA granules in spontaneous reports in Japan is shown in Table 5.

Table 5. Occurrence of photosensitivity-related events for ALA granules in spontaneous adverse drug reactions reports in Japan

No	Year of onset	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with "drugs known to cause photosensitivity" or food containing SJW
1	2017	Photosensitivity reaction	Serious*1	Recovering	120 hours	20 hours and 15 minutes	Telmisartan/amlodipine besilate, esomeprazole magnesium hydrate, amlodipine besilate

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No	Year of onset	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with "drugs known to cause photosensitivity" or food containing SJW
2	2020	Hyperhidrosis	Non-serious	Recovered	Unknown	1 hour and 40 minutes	Amlodipine besilate
3	2019	Rash	Non-serious	Recovered	Unknown	Immediately after administration	None
4	2019	Pruritus	Non-serious	Recovered	Unknown	The day of administration	Unknown
5	2018	Rash	Non-serious	Recovered	Unknown	The day of administration	Unknown
6	Unknown	Rash	Non-serious	Recovered	Unknown	2 days	Levofloxacin hydrate
7	2019	Photosensitivity reaction	Non-serious	Recovered	48 hours	54 hours	None
8	2019	Photosensitivity reaction	Non-serious	Recovered	Unknown	Unknown	None
9	2018	Photosensitivity reaction	Non-serious	Recovered	Unknown	Unknown	Unknown
10	2019	Photosensitivity reaction	Non-serious	Recovered	Unknown	Unknown	Unknown
11	2021	Photosensitivity reaction	Non-serious	Recovered	Unknown	Unknown	Unknown
12	Unknown	Rash	Non-serious	Recovered	Unknown	Unknown	Unknown
13	2018	Photosensitivity reaction	Non-serious	Recovering	Unknown	Unknown	None
14	2018	Photosensitivity reaction	Non-serious	Recovering	Unknown	Unknown	Unknown
15	Unknown	Rash	Non-serious	Recovering	Unknown	Unknown	Unknown
16	2019	Contact dermatitis	Non-serious	Unknown	Unknown	1 hour	Amlodipine besilate
17	Unknown	Photosensitivity reaction	Non-serious	Unknown	Unknown	2 to 3 days	Unknown
18	Unknown	Photosensitivity reaction	Non-serious	Unknown	Unknown	2 to 3 days	Unknown
19	Unknown	Photosensitivity reaction	Non-serious	Unknown	Unknown	2 to 3 days	Unknown
20	Unknown	Photosensitivity reaction	Non-serious	Unknown	Unknown	2 to 3 days	Unknown

*1The serious case was treated with steroids and white petroleum and the outcome was recovering.

(3) Occurrence of photosensitivity-related events in which ALA was used for visualization of malignant glioma overseas is shown in Table 6.

Table 6. Occurrence of photosensitivity-related events of ALA in adverse drug reactions reports overseas

No	Year of onset	Country	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with “drugs known to cause photosensitivity” or food containing SJW
1	2017	DE	Photosensitivity reaction	Serious[*1]	Recovered	Unknown	The day of administration	Unknown
2	2018	US	Photosensitivity reaction	Non-serious	Recovered	Unknown	Immediately after administration	Unknown
3	2019	US	Eye irritation, ocular hyperaemia	Non-serious	Recovered	Unknown	24 to 48 hours	Unknown
4	2019	US	Erythema, feeling hot	Non-serious	Recovered	Unknown	Unknown	Prochlorperazine
5	Unknown	US	Photosensitivity reaction	Non-serious	Recovered	Unknown	Unknown	Unknown
6	2021	ES	Photosensitivity reaction	Non-serious	Recovering	Unknown	Unknown	Unknown
7	2015	ES	Photosensitivity reaction, urticarial rash	Non-serious	Recovering	Unknown	Unknown	Omeprazole
8	2020	US	Erythema, skin exfoliation, burning sensation, blister	Non-serious	Recovering	Unknown	Unknown	Unknown
9	2012	FR	Erythema	Non-serious	Not recovered	Unknown	Within 24 hours	Unknown
10	2020	TW	Rash	Non-serious	Not recovered	Unknown	Unknown	Unknown
11	2020	US	Erythematous rash, blister	Non-serious	Unknown	Unknown	Within 24 hours	Hydrochlorothiazide
12	2017	NL	Erythematous rash	Non-serious	Unknown	Unknown	Within 24 hours	Unknown
13	2016	DK	Sunburn	Non-serious	Unknown	Unknown	Unknown	Unknown
14	2021	US	Erythema	Non-serious	Unknown	Unknown	Unknown	Unknown

No	Year of onset	Country	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with “drugs known to cause photosensitivity” or food containing SJW
15	2018	GB	Erythema	Unknown	Recovered	Unknown	Unknown	Unknown
16	2020	US	Erythema	Unknown	Unknown	Unknown	After 2 weeks	Unknown
17	2013	SE	Photosensitivity reaction	Unknown	Unknown	With exposure to light	Unknown	Unknown

*1 The serious case was mistakenly administered with ALA intravenously and photosensitive erythema occurred on the upper body of the patient on the day of administration. The patient recovered by administration of antihistamine.

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Attachment 6 Occurrence of photosensitivity in drug use-results survey

(1) Incidence of photosensitivity-related events for Alabel Oral in drug use-results survey is shown in Table 7.

Table 7. Occurrence of photosensitivity-related events for Alabel oral in drug use-results survey

No	Year of onset	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with drugs known to cause photosensitivity. *1
1	2013	Photosensitivity reaction	Non-serious	Recovering	48 hours	1day	Unknown *2

*1 Limited to antineoplastic drugs indicated for malignant glioma which are known to cause photosensitivity

*2 Details for the case are unknown, although allergy to tape products was described as a factor for photosensitivity other than this drug.

(2) Occurrence of photosensitivity-related events in drug use-results survey of Alaglio granules is shown in Table 8.

Table 8. Occurrence of photosensitivity-related events in drug use-results survey of Alaglio granules

No	Year of onset	Adverse reactions (PT)	Seriousness	Outcome	Shading period	Time from administration to onset	Co-administration with “drugs known to cause photosensitivity”.
1	2017	Photosensitivity reaction	Non-serious	Recovered	18 hours	18 hours	Fenofibrate, valsartan/hydrochlorothiazide, atorvastatin calcium hydrate, clopidogrel sulfate
2	2018	Pruritus	Non-serious	Recovered	48 hours	The day of administration	Benidipine hydrochloride, pravastatin sodiumravastatin sodium
3	2018	Erythema	Non-serious	Recovered	48 hours	Next morning	None
4	2018	Pruritus	Non-serious	Recovered	95 hours	Next day	None
5	2018	Urticaria	Non-serious	Recovered	72 hours	3 days	None
6	2018	Photosensitivity reaction	Non-serious	Recovered	None	None	Sodium ferrous citrate

7	2017	Photosensitivity reaction	Non-serious	Recovering	72 hours	15 hours	None
8	2018	Erythema	Non-serious	Recovering	1 hour	Next day	None

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Attachment 7. Search conditions for published literature on photosensitivity occurring after ALA administration (PubMed, Google search, CiNii Articles)

The search strategy was as follows:

- Keywords listed as A:, B:, C:, in Table 1 and 2 were combined with “AND.”
- For the search of clinical studies, those on administration routes other than oral were excluded from the report.
- For the search of non-clinical studies, studies found by the search were examined for the presence or absence of the effects of co-administration of 5-ALA and other drugs on phototoxicity.
- For the search of pharmacological studies, those that evaluate the efficacy of photodynamic therapy using 5-ALA on various cancer cells were excluded from the report both *in vivo* and *in vitro* because such evaluations were not considered to be evaluations of photosensitivity.

Table 1 Search conditions for English research papers

Search sites: PubMed, Google search

Keywords for clinical research papers	Keywords for non-clinical research papers
A: δ-aminolevulinic acid / 5-aminolevulinic acid / aminolevulinic acid / 5-ALA B: phototoxic / phototoxic reaction / photosens / photosensitivity / sunburn C: safety / side effect / adverse / adverse reaction / adverse event	A: δ-aminolevulinic acid / 5-aminolevulinic acid / aminolevulinic acid / 5-ALA B: phototoxic / phototoxic reaction / photosens / photosensitivity / sunburn C: animal /cell / *in vivo* / *in vitro* / pharmacology /pharmacologic

Table 2 Search conditions for Japanese research papers

Search sites: CiNii Articles, Google search

Keywords for clinical research papers	Keywords or non-clinical research papers
A: アミノレブリン酸 / 5-ALA B: 光線過敏 / 光感受性 / サンバーン C: 安全性 / 副作用	A: アミノレブリン酸 / 5-ALA B: 光毒性 / 光線過敏/ 光感受性 C: 動物 / 細胞 / *in vivo* / *in vitro* / 薬理

Attachment 8. Search conditions for published literature on photosensitivity occurring after ALA administration (MEDLINE, JAPIC-Q)

1. Overseas literature

The search strategy for overseas literature was as follows:
Database: MEDLINE, Search period: 1900/1/1 to 2020/11/25

No	Search formula	Notes
1	FAV, DCOM (19000101-20201125) AND FDB(MEDLINEPROF)	Search period and database specified
S1	TI, AB ("5-ALA" OR "aminol [*1] evulinic acid*" OR "aminol [*1] evulinate*" OR "deltaaminol [*1] evulinic acid*" OR "Alabel" OR " Gliolan" OR "Alaglio")	5-ALA (TIAB)
S3	MESH.X("Aminolevulinic Acid")	5-ALA (MeSH)
S4	TI, AB ("photosensitivity" OR "photosensitive disorder [*1]" OR "photodermatosis" OR "photodermatoses" OR "photodermatitis" O R ("photo*" p/2 ("reaction [*1]" OR "dermatosis" OR "dermatoses " OR "dermatitis"))) OR TI, AB (("sun" OR "sunlight" OR "UV" OR "ultraviolet" OR "light") AND ("reaction [*1]" OR "dermatosis" OR "dermatoses" OR "dermatitis"))	Photosensitivity (TIAB)
S5	MESH. # ("Photosensitivity Disorders" LNK CI)	Photosensitivity (MeSH)
S6	TI, AB ("case" n/2 "report [*2]")	Case report (TIAB)
S7	DTYPE ("Case Reports")	Case report (MeSH/mode of publication)
S8	S1 AND (S2 OR S3) AND (S4 OR S5) AND (S6 OR S7)	Search results

2. Japanese literature

The search strategy of Japanese literature was as follows:
Search period: 2013/3/25 (approval date) to 2020/11/30
Database: JAPIC-Q

Search formula:

CN07
アラベル (5-Ala,Aminolevulinic acid)
<("5 aminolevulinic acid*/DR/07" OR "5 aminolevulinic acid*/DR/09" OR "aminolevulinic acid*/DR/07" OR "aminolevulinic acid*/DR/ 09") LINK (副作用／FW/ 01 OR 感染症/FW/01 OR 有害事象/FW/01 OR 自殺企図/FW/01 OR 毒性等/FW/01 OR 相互作用/FW/01 OR 過量投与/FW/01 OR 誤用乱用/FW/01 OR 医療過誤/FW/01 OR 職業上の曝露/FW/01 OR 品質/FW/01 OR その他/FW/01 OR 副作用軽減/FW/01 OR 有効性欠如/FW/01 OR 無効/FW/01 OR 妊婦/FW/01 OR 授乳婦/FW/01 OR 18 歳以下/FW/01 OR 適応外使用/FW/01 OR 偽造薬/FW/01 OR 予想外治療効果/FW/01)>

Articles in which ”光線過敏症の記載” was not found were excluded.

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Attachment 9: Search conditions for descriptions in Japanese and overseas standard textbooks and clinical practice guidelines

1. Investigation of bladder cancer textbooks, etc.

・ Since Japan is the only country that has approved “Visualization of non-muscle invasive bladder cancer during transurethral resection of the bladder tumor” as an indication of oral administration of 5-ALA hydrochloride, textbooks, etc. published in 2017 or later were searched using keywords listed as A;, B;, and C; below combined with “AND.”

Search site: The search site of the National Diet Library, Google search
Keywords: A, 泌尿器科/ 膀胱癌, B: アミノレブリン酸/ 5-ALA, C: 図書/ 書籍/ 参考書/ 冊子/ ガイドライン

2. Investigation of malignant glioma textbooks, etc.

・ Japanese textbooks, etc.
・ Keywords listed as A;, B;, C;, below were combined with “AND,” and textbooks found by the search were examined for descriptions concerning 5-ALA.

Search site: The search site of the National Diet Library, Google search
Keywords: A; 脳神経外科/ 脳腫瘍/ 悪性神経膠腫, B; アミノレブリン酸/ 5-ALA, C; 図書/ 書籍/ 参考書/ 冊子/ ガイドライン

・ Overseas textbooks, etc.

Search site: Google search
Keywords: A; urology / bladder cancer / bladder tumor, B; aminolevulinic acid / 5-ALA, C; book / textbook / guideline

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp