Pharmaceuticals and Medical Devices Safety Information

No. 390 March 2022

Table of Contents

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Pharmaceuticals and Medical Devices Safety Information

No. 390 March 2022

Ministry of Health, Labour and Welfare
Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
ALA	Aminolevulinic acid hydrochloride
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PDD	Photodynamic diagnosis
PMDA	Pharmaceuticals and Medical Devices Agency
PPIX	Protoporphyrin IX
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SJW	St. John's Wort

1

Revision of Precautions for Aminolevulinic Acid Hydrochloride

1. Introduction

Aminolevulinic acid hydrochloride (brand name: Alabel Oral 1.5 g, Alaglio Divided Granules 1.5 g, hereinafter referred to as “ALA”) is a photodynamic diagnosis (PDD) agent. The ALA oral agent (brand name: Alabel Oral 1.5 g) was approved for marketing on March 25, 2013 for the indication of “visualization of malignant tissue during malignant glioma resection” and the granule formulation of ALA was approved for marketing on September 27, 2017 as indicated for “visualization of non-muscle invasive bladder cancer during transurethral resection of the bladder tumor”. Because of photosensitivity as a known adverse reaction to ALA, precaution for photosensitivity has been in place in the Japanese package inserts of the ALA oral agent and the granule formulation (hereinafter referred to as the “ALA preparations”) since the time of approval for ALA, with drugs known to cause photosensitivity and food containing St. John’s Wort (hereinafter referred to as “SJW”) noted as contraindications and contraindications for co-administration.

Recently, precautions for ALA such as contraindications and contraindications for co-administrations have been revised based on the deliberation in the 24th Fiscal year (FY)2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as “the Subcommittee on Drug Safety”) held on December 20, 2021. This section will introduce the details of the revision.

2. Background

ALA is metabolized in vivo to protoporphyrin IX (hereinafter referred to as “PPIX”), which is a photosensitive substance, and accumulates in a tumor-specific manner. In the operative filed, ALA visualizes tumor sites by utilizing the nature of PPIX that emits red fluorescent light when excited by blue light. Because of photosensitivity as a known adverse reaction to ALA, precaution for photosensitivity has been in place in the Japanese package inserts of ALA preparations since the time of approval for ALA. Besides, drugs known to cause photosensitivity and food containing SJW have been 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.

On June 7 and on July 1, 2021, requests for revision of precautions were submitted to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter the “Pharmaceutical Safety Division”) from the Japanese Urological Association and Japan Urological Photodynamic Society, and from Japan Photodynamic Neurosurgical Society, respectively. The former requested that the contraindication for co-administration with “drugs known to cause photosensitivity” be revised to precaution for co-administration for the ALA granule formulation and the latter that the contraindication for co-administration with “drugs known to cause photosensitivity” be revised to precaution for co-administration for the ALA oral agent, as well as that the 2 weeks after administration as the period of contraindication for co-administration be changed to 24 hours before and after administration as the period of caution for co-administration for the ALA oral agent.

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 hypersensitivity” 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 and 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 the revision of the current contraindications for co-administration to 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.

Taking into account the requests from the academic societies mentioned above, MHLW decided to consider revision of the contraindications and contraindications for co-administration, etc.

3. Deliberation by the Subcommittee on Drug Safety

The results of the investigation of the current description in Japanese and overseas guidelines as well as in overseas package inserts, results of the use-results survey, or the current status of adverse reaction reports/studies/reports on measures etc. are as follows.

(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.

- The “drugs known to cause photosensitivity” include drugs that are frequently used after neurosurgery as well as those used in general clinical practice for prevention of infections after transurethral surgery. Contraindicating these drugs for co-administration is hampering actual clinical practice.
- The current IMPORTANT PRECAUTIONS section includes a cautionary statement that patients should avoid intense light at least for 48 hours following administration of ALA, thereby addressing the risk reduction of photosensitivity.
- 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.

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

- 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.
- While the request specified 24 hours following administration as the maximum duration, considering the period of at least 48 hours following administration of ALA to avoid intense light specified in the IMPORTANT PRECAUTIONS section, precaution is also necessary for co-administration with “drugs known to cause photosensitivity” or food containing SJW for the same length of time. Of note, the specified light interception time reflects a reported fact that the reduced minimal erythema dose (MED), as an indication of enhanced photosusceptibility,

returned to the baseline in 48 hours following administration and that some of the adverse events related to photosensitivity observed in overseas clinical studies had developed 2 days after administration of this drug.

Given the above results of the investigation, the Subcommittee on the Drug Safety concluded that the package inserts of ALA preparations may be revised by reinstating the current contraindications for co-administration with the “drugs known to cause photosensitivity” and food containing SJW as precautions for co-administration, with the period of special caution for co-administration revised to 48 hours after administration of ALA.

4. Closing remark

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the revised electronic package inserts for a careful decision on the co-administration of aminolevulinic acid hydrochloride with “drugs known to cause photosensitivity” or food containing SJW. Continued cooperation by healthcare professionals for proper use of this drug would be appreciated.

[References]

- Materials 1-1 to 1-4 of the 24th FY 2021 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on December 20, 2021)
  https://www.mhlw.go.jp/stf/newpage_22790.html (only in Japanese)
- Revision of Precautions (PSEHB/PSD Notification No. 0106-1 dated January 6, 2022)
  https://www.mhlw.go.jp/content/000875491.pdf (only in Japanese)
  English translation by PMDA (January 6, 2022)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0009.html

2
Revision of Precautions (No.330)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated January 6, February 3, 2022.

1 Other diagnostic agents
Aminolevulinic acid hydrochloride

Brand name [1] Alabel Oral 1.5 g (Nobelpharma Co., Ltd.), [2] Alaglio Divided Granules 1.5 g (SBI Pharmaceuticals Co., Ltd.)

[Under Old instructions]

Contraindications (deleted)

Drug Interactions

Contraindications for Co-administration (deleted)

Precautions for Co-administration (newly added)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs known to cause photosensitivity: Tetracyclines, sulfonamides, or fluoroquinolones, etc. Food containing St. John's Wort	Caution should be exercised for photosensitivity that may occur. For 48 hours after administration of this drug particularly, administration of the drugs or ingestion of the food listed on the left-hand side should preferably be avoided as much as possible.	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 side may enhance photosensitivity.

2 Contraceptives
Levonorgestrel (preparations indicated for emergency contraception)

Brand name Norlevo Tablet 1.5 mg (Aska Pharmaceutical Co., Ltd.), and the others

[Under Old instructions]

Important Precautions Prior to administration of this drug, the absence of pregnancy should be confirmed. In addition, the current and past presence or absence of abnormal hepatic function and heart or renal diseases should be confirmed through an interview or other appropriate measures.

Use during Pregnancy, Delivery or Lactation This drug should not be administered to pregnant women. [This drug is not effective in an existing pregnancy.]

(newly added) An observational study conducted overseas has reported that there were no differences in the incidence of foetal malformation, miscarriage, or any other adverse pregnancy outcomes in pregnancies, despite taking levonorgestrel as an emergency contraceptive compared with pregnancies without exposure to levonorgestrel.

(newly added) Other Precautions
External genital abnormality has been reported in infants born to women

	who used other progestogen preparations, although not for the purpose of emergency contraception.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	This drug is indicated for avoidance of pregnancy sought after sexual intercourse. For planned contraception, more effective contraceptive options such as oral contraceptives should be used whenever possible. Pregnancy may not be avoided following administration of this drug. Instructions on appropriate options for routine contraception should be given by the healthcare provider. Prior to administration of this drug, the following should be confirmed: · The person is not pregnant. ·The current and past presence or absence of abnormal hepatic function and heart or renal diseases through an interview or other appropriate measures.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.4 Patients with Reproductive Potential**	(deleted)
9.5 Pregnant Women	This drug should not be administered. This drug is not effective in an existing pregnancy.
(newly added)	An observational study conducted overseas has reported that there were no differences in the incidence of foetal malformation, miscarriage, or any other adverse pregnancy outcomes in pregnancies, despite taking levonorgestrel as an emergency contraceptive compared with pregnancies without exposure to levonorgestrel.
(newly added)	15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Use External genital abnormality has been reported in infants born to women who used other progestogen preparations, although not for the purpose of emergency contraception.

3

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 31 January 2022)
◎: Products for which EPPV was initiated after January 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Tocilizumab (genetical recombination) *1 / Actemra for Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	January 21, 2022
◎	3-Iodobenzylguanidine (^{131}I) / Raiatt MIBG-I 131 Injection	FUJIFILM Toyama Chemical Co., Ltd.	January 18, 2022
	Molnupiravir / Lagevrio Capsules 200 mg	MSD K.K.	December 24, 2021
	Prasugrel hydrochloride*2 / Efient Tablets 2.5 mg, 3.75 mg	Daiichi Sankyo Co., Ltd.	December 24, 2021
	Azilsartan / Azilva Granules 1%, Azilva Tablets 10 mg, 20 mg, 40 mg	Takeda Pharmaceutical Company Limited.	December 16, 2021
	Abrocitinib / Cibinqo Tablets 50 mg, 100 mg, 200 mg	Pfizer Japan Inc.	December 13, 2021
	Selpercatinib / Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	December 13, 2021
	Somapacitan (genetical recombination) / Sogroya Subcutaneous Injection 5 mg, 10 mg	Novo Nordisk Pharma Ltd.	December 10, 2021
	Enfortumab vedotin (genetical recombination) / Padcev for I.V. infusion 30 mg	Astellas Pharma Inc.	November 30, 2021
	Progesterone / F-meno capsules 100 mg	Fuji Pharma Co., Ltd.	November 29, 2021

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Avalglucosidase alfa (genetical recombination) Nexviazyme for I.V. Infusion 100 mg	Sanofi K.K.	November 26, 2021
Tucidinostat[*3] Hiyasta tablets 10 mg	Huya Japan G.K.	November 25, 2021
Empagliflozin[*4] Jardiance Tablets 10 mg	Boehringer Ingelheim Japan, Inc.	November 25, 2021
Anifrolumab (genetical recombination) Saphnelo for I.V. infusion 300 mg	AstraZeneca K.K.	November 25, 2021
Relebactam hydrate/imipenem hydrate/cilastatin sodium Recarbrio Combination for Intravenous Drip Infusion	MSD K.K.	November 9, 2021
Casirivimab (genetical recombination), Imdevimab (genetical recombination) Ronapreve Injection Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	November 5, 2021
Tucidinostat Hiyasta tablets 10 mg	Huya Japan G.K.	October 20, 2021
Follitropin delta (genetical recombination) Rekovelle Pen for S.C. Injection 12 μg, 36 μg, 72 μg	Ferring Pharmaceuticals Co., Ltd.	October 1, 2021
Sotrovimab (genetical recombination) Xevudy for Intravenous Injection 500 mg	GlaxoSmithKline K.K.	September 29, 2021
L-Lysine hydrochloride, L-arginine hydrochloride Lysakare Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
Lutetium (^{177}Lu) hepato Lutathera Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
Midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	September 27, 2021
Rituximab (genetical recombination)[*5] Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	September 27, 2021
Sacubitril valsartan sodium hydrate[*6] Entresto Tablets 100 mg, 200 mg	Novartis Pharma K.K.	September 27, 2021
Sirolimus[*7] Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	September 27, 2021
Ibrutinib[*8] Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	September 27, 2021
Secukinumab (genetical recombination) [1] Cosentyx for s.c. injection 150 mg syringe [2] Cosentyx for s.c. injection 150 mg pen [3] Cosentyx for s.c. injection 75 mg syringe	Novartis Pharma K.K.	September 27, 2021
Dinutuximab (genetical recombination) Unituxin I.V. injection 17.5 mg/5 mL	Ohara Pharmaceutical Co., Ltd.	September 22, 2021
Imeglimin hydrochloride Twymeeg Tablets 500 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 16 2021

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Vericiguat Verquvo tablets 2.5 mg, 5 mg, 10 mg	Bayer Yakuhin Ltd.	September 15, 2021
Fremanezumab (genetical recombination) Ajovy Syringes for S.C. Injection 225 mg	Otsuka Pharmaceutical Co., Ltd.	August 30, 2021
Givosiran sodium Givlaari Subcutaneous Injection 189 mg	Alnylam Japan K.K.	August 30, 2021
Upadacitinib hydrate*9 Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	August 25, 2021
Dapagliflozin propylene glycolate hydrate*10 Forxiga 5 mg, 10 mg tablets	AstraZeneca K.K.	August 25, 2021
Selexipag*11 Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	August 25, 2021
Fentanyl citrate*12 Fentos Tapes 0.5 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	August 25, 2021
Upacicalcet sodium hydrate Upasita IV Injection Syringe for Dialysis 25 μg, 50 μg, 100 μg, 150 μg, 200 μg, 250 μg, 300 μg	Sanwa Kagaku Kenkyusho Co., Ltd.	August 20, 2021
Teduglutide (genetical recombination) Revestive 3.8 mg for S.C. Injection	Takeda Pharmaceutical Company Limited.	August 18, 2021
COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector) Vaxzevria Intramuscular Injection	AstraZeneca K.K.	August 16, 2021
Erenumab (genetical recombination) Aimovig Subcutaneous injection Pens 70 mg	Amgen K.K.	August 12, 2021
Risdiplam Evrysdi Dry Syrup 60 mg	Chugai Pharmaceutical Co., Ltd.	August 12, 2021
Tazemetostat hydrobromide Tazverik tablets 200 mg	Eisai Co., Ltd.	August 16, 2021
Larotrectinib sulfate Vitrakvi oral solution 20 mg/mL	Bayer Yakuhin Ltd.	August 6, 2021
Simoctocog alfa (genetical recombination) Nuwiq For I.V. Injection 250, 500, 1000, 2000, 2500, 3000, 4000	Fujimoto Pharmaceutical Corporation	August 2, 2021

*1 SARS-CoV-2 pneumonia (limited to patients requiring oxygen intervention)

*2 Prevention of recurrence of ischaemic cerebrovascular disease following the former appearance of ischaemic cerebrovascular disease (associated with large-artery atherosclerosis or small-vessel occlusion) (restricted to cases with a high risk of ischaemic stroke).

*3 Relapsed or refractory peripheral T-cell lymphoma

*4 Chronic heart failure (only in patients who are receiving standard of care for chronic heart failure)

*5 Systemic scleroderma

*6 Hypertension

*7 Refractory lymphatic diseases (lymphangioma (lymphatic malformation), lymphangiomatosis, Gorham's disease, lymphangiectasia)

*8 Chronic graft versus host disease after haematopoietic stem cell transplantation (when steroids are not sufficiently effective)

*9 Atopic dermatitis that has not responded adequately to conventional treatments

*10 Chronic kidney disease

*11 Chronic thromboembolic pulmonary hypertension inoperable or persistent/recurrent after interventional treatment

*12 Pain relief in cancers accompanied by moderate to severe pain difficult to treat with non-opioid analgesics (limited to use as a switch from other opioid analgesics)