GLEOIAN™ (aminolevulinic acid hydrochloride) for oral solution

IMPORTANT PRECAUTIONS
- Phototoxic reactions: Do not administer phototoxic drugs (St. John’s wort, griseofulvin, thiazide diuretics, safinamyl, phenoxybenzamine, sulphonamides, quinolones and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period. Reduce exposure to sunlight or room lights for 48 hours after oral administration of GLEOIAN. (5.1, 17)
- Risk of misinterpretation: Non-fluorescing tissue in the surgical field does not rule out the presence of tumor. (5.2, 14)

ADVERSE REACTIONS
- Adverse reactions occurring in >1% of patients in the week following surgery were pyrexia, hypotension, nausea, and vomiting. (6.1)
- Adverse reactions occurring in <1% of patients in the first 6 weeks after surgery were: chills, photosensitivity reaction, solar dermatitis, hypotension, abnormal liver function test, and diarrhea. (6.1)
- Neurologic events related to the surgical procedure occurred in 29% of patients and included: aphasia, hemiparesis, hemiphenia, headache, seizure, hemiplegia, monoparesis, hypotension, and brain edema. (6.1)
- Elevated liver enzymes occurred in clinical studies. There were no cases of liver failure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NXDIX toll-free at (844) 517-5252 and adverseevents@nxedcorp.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions
Fluorescence may be seen in areas of tumor and hence should not be used in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. (1)

DOSAGE AND ADMINISTRATION
For oral solution: 1,500 mg aminolevulinic acid hydrochloride (ALA HCl) lyophilized powder, equivalent to 1,370 mg aminolevulinic acid per vial. The reconstituted aminolevulinic acid hydrochloride solution contains 30 mg/ml and is clear and colorless to slightly yellowish in color. (3)

Contraindications
- Hypersensitivity to aminolevulinic acid (ALA) or porphyrins. (4, 5.3, 6.2)
- Acute or chronic types of porphyria. (4)

Indications and Usage
GLEOIAN is indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. (1, 5.1)

Full Prescribing Information
1. Indications and Usage
GLEOIAN is indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. (1)

2. Dosage and Administration
2.1 Recommended Dose
For oral use only
- The recommended oral dose of reconstituted GLEOIAN is 20 mg/kg body weight. More than 1 vial may be required.

2.2 Reconstitution of GLEOIAN
Gleolan powder must be reconstituted prior to administration by a healthcare provider according to the following instructions:
- Determine the total number of vials needed to achieve the intended dose for the patient according to the equation below (rounded up to the nearest whole vial):

\[ \text{# of vials} = \frac{\text{Patient Body Weight (kg)}}{75 \text{ mg/vial}} \]

- Completely remove the white cap and aluminum crimp seal from each vial.
- Remove and retain the rubber stopper from the vial.
- Using an appropriate volumetric measuring device (e.g., flask, graduated cylinder, dosing syringe), measure 50 ml of drinking water and add to each vial containing 1,500 mg of GLEOIAN.
- Gently swirl the vial to completely dissolve the powder.
- The resulting reconstituted solution (10 mg of GLEOIAN per ml) is clear and colorless to slightly yellowish.
- If required, replace the stopper and store reconstituted solution for up to 24 hours at room temperature prior to administration.

2.3 Gleolan Administration
GLEOIAN is for ORAL USE ONLY. The reconstituted Gleolan solution is to be stored in the refrigerator at 2-8°C (36-46°F) until ready for use and should be used within 24 hours of reconstitution. The reconstituted solution is stable for up to 24 hours when stored at room temperature (25°C). (2.3)

3. Dosage Forms and Strengths
For oral solution: 1,500 mg aminolevulinic acid hydrochloride lyophilized powder, equivalent to 1,370 mg aminolevulinic acid per vial. The reconstituted aminolevulinic acid hydrochloride solution contains 30 mg/ml and is clear and colorless to slightly yellowish in color. (3)

Patent Counseling Information
See Full Prescribing Information for reconstitution information. (2.2)

Full Prescribing Information: Contents
1. Indications and Usage
2. Dosage and Administration
3. Dosage Forms and Strengths
4. Contraindications
5. Warnings and Precautions
6. Adverse Reactions
7. Clinical Trial Experience
8. Use in Specific Populations
9. Pregnancy
10. Lactation

Full Prescribing Information

8.4 Pediatric Use
8.6 General Use
8.7 Patients with Hepatic Impairment
10. OVERDOSAGE

11. DESCRIPTION
11.1 Chemical Properties
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14. CLINICAL STUDIES
15. HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling

17. PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

4. Contraindications
- Hypersensitivity to aminolevulinic acid (ALA) or porphyrins. (see Warnings and Precautions [5.3])
- Acute or chronic types of porphyria, due to potential ineffectiveness of the drug in these patients.

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, safinamyl, phenoxybenzamine, sulphonamides, quinolones and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period. (see Drug Interactions [7.2]). Reduce exposure to sunlight or room lights for 48 hours after administration of GLEOIAN.

5.2 Risk of Misinterpretation
Errors may occur with the use of GLEOIAN for intraoperative visualization of malignant glioma, including false negatives and false positives. Non-fluorescing tissue in the surgical field does not rule out the presence of tumor in patients with glioma (see Clinical Trials [14]). Fluorescence may be seen in areas of inflammation or metastases from other tumor types.

5.3 Hypersensitivity Reactions
Hypersensitivity reactions, including serious hypersensitivity reactions have occurred; these reactions include anaphylactic shock, swelling, and urticaria (see Contraindications [4], Adverse Reactions [6.2]). Always have cardiopulmonary resuscitation personnel and equipment readily available and monitor all patients for hypersensitivity reactions.

6. Adverse Reactions
6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of GLEOIAN is supported by data from 5 open-label clinical studies, which included 127 patients with glioma who received GLEOIAN. Adverse reactions that occurred in >1% of patients in the week following surgery were pyrexia, hypotension, nausea, and vomiting. Adverse reactions occurring in the first 6 weeks after surgery in <1% of patients were: chills, phototoxic reaction, solar dermatitis, hypotension, abnormal liver function test, and diarrhea. One patient experienced respiratory failure due to drug overdose (see Overdosage [10]).

6.2 Neurologic Events
Nervous system disorders occurred in 29% of patients within the first week after surgery. Events occurring in >1% of patients included aphasia (8%), hemiparesis (7.8%), hemianopsia (12%), headache (7.2%), seizure (11%), hemiplegia (11%), monoparesis (11%), and hypersomnia (11%). Brain edema occurred in <1% of patients in the first 6 weeks after surgery. In a randomized clinical trial (Study 3), the numbers of serious neurologic adverse events in the post operative period were higher in patients randomized to ALA fluorescence arm compared to the control arm. An imbalance was notable for the adverse events aphasia, ataxia, convulsion and hemiparesis, and is likely related to the higher amount of brain resection performed in the ALA arm. At longer follow up periods, the numbers between the two arms appeared similar (see Clinical Trials [14]).

Elevated Liver Enzymes
Worsening of ALT and other Toxicity Criteria (TTC) grades in alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) occurred in 15.8% and 11.6%, respectively) within the first week after surgery. Absolute levels ranged from 2 times to greater than 10 times the upper limit of normal (ULN) for each parameter. At week 6, ALT remained elevated in 2.9% of patients (range 2 to greater than 5 X ULN), and GGT was elevated in 7.5% of patients (range 2 to greater than 10 X ULN). No cases of liver failure occurred.
Bioavailability
In 12 healthy subjects, the absolute bioavailability of ALA following the recommended dose of Gleolan solution was 100.0% ± 1.1 with a range of 78.5% to 131.2%. Maximum ALA plasma concentrations were reached with a median of 0.8 hour (range 0.5 – 1.0 hour).

Distribution
In in vitro experiments using ALA concentrations up to approximately 25% of the maximal concentration that occurs in plasma following the recommended dose of Gleolan solution, the mean protein binding of ALA was 72%.

Elimination
Metabolism
Exogenous ALA is metabolized to PpIX, but the fraction of administered ALA that is metabolized to PpIX is unknown. The average plasma AUC of PpIX is less than 6% of that of ALA.

Excretion
In 12 healthy subjects, excretion of parent ALA in urine in the 12 hour following administration of the recommended dose of Gleolan solution was 34 ± 8% (mean ± std dev) with a range of 27% to 57%.

Specific Populations
The effect of renal or hepatic impairment on the pharmacokinetics of ALA following Gleolan administration is unknown.

Drug Interaction Studies
In vitro studies suggest that phenytoin and other anti-convulsants may decrease cellular PpIX accumulation following Gleolan dosing.

ALA is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
No carcinogenicity studies have been conducted with Gleolan.

Mutagenesis
ALA HCI was not mutagenic in the Ames assay, HPRT-V79 mammalian cell mutagenicity test, the peripheral human lymphocyte chromosomal aberration assay and the in vivo mouse micronucleus test when studies were performed in the dark or under subdued lighting.

Impairment of fertility
No fertility studies have been conducted with Gleolan.

14 CLINICAL STUDIES
The efficacy of 20 mg/kg ALA HCI was evaluated in 3 clinical studies (Study 1-3) involving patients, ages 18 to 75 years old, who had a preoperative MRI compatible with high-grade glioma (WHO Grade III or IV) and were undergoing surgical resection.

Study 1 was an open-label study of 13 patients with newly diagnosed high-grade glioma and Study 2 was an open-label study of 36 patients with recurrent high-grade glioma. In Studies 1 and 2, after initial debulking was carried out under white light, biopsies were obtained under fluorescent light from fluorescent and nonfluorescent sites. Presence of fluorescence (positive/negative) was compared to tumor status (true/false) using histopathology as the reference standard. True positives and false positives among fluorescent biopsies and true negatives and false negatives among nonfluorescent biopsies are provided in Table 1.

Study 3 was a randomized, multicenter study in 415 patients with a presurgical diagnosis of high-grade glioma by MRI. Patients were randomized in 1:1 ratio to ALA fluorescence arm or to white light control arm. Biopsies were obtained from tumor-core, tumor-margin and regions just distant to the tumor margins. In 349 patients high grade glioma was confirmed by a blinded central read and histopathology. The remaining patients were diagnosed with metastatic disease, abscess, low-grade glioma or other conditions.

In patients with confirmed high-grade glioma randomized to the ALA fluorescence arm, presence of fluorescence at a biopsy level was compared to tumor status using histopathology as the reference standard (Table 1). In 4 patients with low-grade glioma (WHO Grade I or II) who received ALA-HCl, 9 out of 10 biopsies were false negative.

The extent of resection among patients with confirmed high-grade glioma in the ALA fluorescence arm was compared to that among patients in the control arm, with the ‘completeness’ of resection being determined by a central blinded read of early post-surgical MRI. Percentage of patients who had ‘completeness’ of resection was 64% in the ALA arm and 38% in the control arm, with the difference of 26% [95% CI: (16%, 36%)].